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DELAYS IN THE TREATMENT OF STATUS EPILEPTICUS – EFFECT ON OUTCOME

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ACADEMIC DISSERTATION

To be publicly discussed with the permission of the Faculty of Medicine
of the University of Helsinki, in Lecture Hall 13, Helsinki University Main Building,
Fabianinkatu 33, Helsinki, on 4th of May 2018 at 12 noon

Helsinki, 2018

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Unigrafia oy
Helsinki 2018
ISBN 978-951-51-4172-9 (Paperback)
ISBN 978-951-51-4173-6 (PDF)

To Antti, Salla, Lotta and Nuutti

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LIST OF ORIGINAL PUBLICATIONS

The present thesis is based on the following original publications, referred in the text by Roman numerals I-IV

I. Leena Kämppi, Harri Mustonen, Seppo Soinila. 2013. Analysis of the delay components in the treatment of status epilepticus. Neurocritical Care (2013) 19:10-18.

II. Leena Kämppi, Harri Mustonen, Seppo Soinila. 2015. Factors related to delays in pre-hospital management of status epilepticus. Neurocritical Care (2015) 22:93-104.

III. Leena Kämppi*, Jaakko Ritvanen*, Harri Mustonen, Seppo Soinila. 2015. Delays and factors related to cessation of generalized convulsive status epilepticus. 2015. Epilepsy Research and Treatment (2015)2015:591279.

IV. Leena Kämppi, Kaisa Kotisaari, Harri Mustonen, Seppo Soinila. 2018. The essence of the first 2.5 h in the treatment of generalized convulsive status epilepticus. Seizure (2018) 55:9-16.

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ABBREVIATIONS

ADL	Activities in daily living
AED	Anti-epileptic drug
AIDS	Acquired immune deficiency syndrome
AMI	Acute myocardial infarction
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
ASID	After status ictal discharge
ATP	Adenosine Triphosphate
BS	Burst-suppression
CBI	Complication Burden Index
CCI	Charlson Comorbidity Index
cEEG	Continuous electroencephalogram
CHF	Congestive heart failure
CNS	Central nervous system
ConSEPT	Convulsive Status Epilepticus Paediatric Trial
CPD	Chronic pulmonary disease
CSE	Convulsive Status epilepticus
CT	Computed tomography
CTD	Connective Tissue disease
CVD	Cerebrovascular disease
DA	Data Availability
DBS	Deep Brain Stimulation
DM	Diabetes Mellitus
DNT	Door-to-needle-time
EcLIPSE	Emergency Treatment with Levetiracetam or Phenytoin in SE in Children
ED	Emergency department
eEEG	Emergent EEG
EEG	Electroencephalogram
ECG	Electrocardiogram
EMS	Emergency medical service
EMSE	Epidemiology-Based Mortality Score in Status Epilepticus
END-IT	Encephalitis, NCSE, Diazepam resistance, Image, Tracheal intubation - score
ER	Emergency Room

ESETT	Established Status Epilepticus Treatment Trial
FSE	Febrile status epilepticus
GABA	Gamma-aminobutyric acid
GCSE	Generalized convulsive status epilepticus
GOS	Glasgow outcome scale
GPD	Generalized periodic discharge
GSE	Generalized status epilepticus
HUCH	Helsinki University Central Hospital
ICD-10	International classification of diseases version 10
ICU	Intensive Care Unit
ILAE	International League Against Epilepsy
IQR	Interquartile range
iv.	Intravenous
IVAD	Intravenous anesthetic drug
LPD	Lateralized periodic discharge
L_{WAS}	Weighted Accuracy Score
MI	Myocardial infarction
MRI	Magnetic resonance imaging
mRS	Modified Rankin Scale
MS Access	Microsoft Access
mSTESS	Modified STESS
NCSE	Non-convulsive status epilepticus
NIHSS	National Institute of Health Stroke Scale
NMDA	N-methyl-D-Aspartate
non-RSE	non-refractory status epilepticus
OST	On-scene-time
PME	Progressive myoclonic epilepsy
PRIS	Propofol infusion syndrome
PVD	Peripheral vascular disease
RAMPART	Rapid Anticonvulsant Medication Prior to Arrival Trial
ROC	Receiver Operating Characteristic
RSE	Refractory status epilepticus
SD	Standard deviation
SE	Status epilepticus
SRSE	Super-refractory status epilepticus

STESS	Status Epilepticus Severity Score
TCP	Total convulsion period
TLE	Temporal lobe epilepsy
TPP	Total pre-status period
VNS	Vagus nerve stimulation

ABSTRACT

Leena Kämppi, Delays in the treatment of status epilepticus – effect on outcome. University of Helsinki: Doctoral Programme in Clinical Research

Status epilepticus (SE), i.e. prolonged epileptic seizure, is a life-threatening medical emergency, which is associated with high mortality and morbidity. International guidelines suggest early and efficient treatment. Thus, long duration of SE is one of the main predictors of poor prognosis and the only prognostic factor that can be affected by shortening the delays in the treatment. However, studies on delays, implementation of treatment guidelines and the effect of delays on outcome are scarce.

The aim of this thesis was to systematically investigate delays in the treatment of SE and factors related to the delays along the whole treatment chain. We also aimed at clarifying the effect of delays on the outcome and at identifying the significant delays related to outcome in order to propose evidence-based targets for streamlining the SE treatment protocol.

The material of this retrospective study consists of 82 consecutive SE patients treated in a tertiary hospital emergency department over two years. Delays, patient characteristics and parameters related to treatment chain were identified and their relations, correlations and effects were investigated.

The results of this thesis reveal that the delays in the treatment of SE are unacceptably long and exceed markedly the suggested time frames in the guidelines. Fulfilment of the suggested SE treatment algorithm is frequently hampered by failing recognition of SE at onset, also by professionals, which may increase the delays in consecutive parts of the treatment chain. Delays seem to be more significant determinants of SE duration than previously established outcome predictors. Additionally, various long delays in the treatment (second- and third-stage medication, diagnostic and tertiary hospital delays) increase the risk of mortality and poor functional outcome at hospital discharge and since the predictive cut-off point of these delays lies under 2,5 hours, the focus of protocol streamlining should be in the pre-hospital phase of the treatment. However, none of the delays are independent risk factors for poor

outcome, which reflects the dynamism of SE, but also demonstrates that every step of the treatment chain needs to be optimized.

In conclusion, we propose that generation of simplified criteria for suspicion of an imminent SE and streamlining pre-hospital treatment chain are advocated. We suggest amendments to the protocol, such as triaging suspected SE patients with highest priority, recruiting physician-based EMS units upon primary alarm, administration of second-stage medication out-of-hospital and transportation of SE patients exclusively to hospitals with neurological expertise. Also, improvement of diagnostic possibilities on emergency site should be considered.

1 REVIEW OF THE LITERATURE

1.1 Status epilepticus

Status epilepticus (SE) is the most extreme form of an epileptic seizure. It is considered to be a life-threatening neurological emergency situation, which requires immediate treatment actions to cease the excessive electric activity in the brain. Even when treated with the best medical practices, it may result in substantial morbidity and mortality. 4 - 16 % of the epileptic patients experience SE during their lives[1].

1.1.1 Definition

Already in 1867 Trousseau perceived that "in SE, when convulsive condition is almost continuous, something special takes place which requires an explanation". In 1904 SE was defined as seizures occurring so frequently that "coma and exhaustion are continuous between the seizures"[2]. SE was included in the classification of seizures by the International League Against Epilepsy (ILAE) in 1970. It was defined as a "seizure that persists for a sufficient length of time or is repeated frequently enough to produce a fixed and enduring condition"[3]. Over the following few decades animal studies demonstrated that continuous seizure lasting over 30 minutes may result in permanent neuronal damage[4,5]. In the early 1990's the most commonly used criterion for duration of seizures qualifying as SE was 30 minutes[6-8]. For decades the definition of SE was: 1) continuous seizure activity lasting over 30 minutes, or 2) two or more sequential seizures without full recovery of consciousness between seizures. That definition was easy to use, but since its theoretical grounds became questionable, in 1999 a new operational definition based on seizure duration over 5 minutes was proposed for time limit of SE[9]. Clinical data showing that spontaneous cessation of generalized convulsive seizures is unlikely after 5 minutes of convulsion[10,11], and increased understanding of the pathophysiology of SE necessitated reformed definition and classification of SE, which was published in 2015[12].

According to the current definition[12], "SE is a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms which lead to abnormally prolonged seizures (after time

point t1). It is a condition that can have long-term consequences (after time point t2), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures". Beyond the time point t1, the seizure should be regarded as "continuous seizure activity" and time point t2 refers to the time after which ongoing seizure activity may result in long-term consequences. For convulsive (tonic-clonic) SE the best estimates for t1 and t2, based on animal experiments and clinical research, are 5 and 30 minutes, respectively. For other types of SE, time points remain undetermined due to lack of scientific evidence.

1.1.2 Classification and clinical manifestation

In the classification of SE, the purpose of the diagnostic axes is to provide a framework for clinical diagnosis, investigations and therapeutic approaches[3,13]. In the first classification (ILAE 1970)[3] the axes included: (I) clinical seizure type, (II) electroencephalographic ictal and interictal expression, (III) anatomic substrate, (IV) etiology and (V) age. In 1981[14] in the revised classification axes were reduced to (I) seizure type and (II) EEG expression.

Newly revised diagnostic classification system of SE[12] includes four axes: (I) semiology, (II) etiology, (III) eletroencephalography (EEG) correlates, and (IV) age. Semiology contains two main taxonomic criteria: 1) presence or absence of prominent motor symptoms, 2) degree of impaired consciousness. Etiology is divided into two categories: 1) Known etiology (former symptomatic) and 2) Unknown etiology (including former cryptogenic). EEG correlates are denoted by the descriptors of EEG: name of pattern, morphology, location, time-related features, modulation, and effect of intervention. Age is divided into neonatal period, infancy, childhood, adolescence and adulthood (>12 to 59 years), and elderly age (≥60 years).

According to the semiological criteria, the main types of SE can be divided into generalized convulsive SE (GCSE) (prominent motor manifestation with impaired consciousness), focal convulsive SE (focal CSE) (prominent motor manifestation with normal or slightly altered mental status), generalized non-convulsive SE (NCSE) (impaired consciousness without prominent motor manifestation) and focal NCSE (normal or slightly altered mental status without prominent motor manifestations).

1.1.3 *Refractoriness*

Status epilepticus in considered refractory (RSE) to treatment if the seizure continues after treatment with first- and second-stage medications and the patient needs anesthetic (third-stage) treatment in the intensive care unit (ICU)[15,16].

The term super-refractory status epilepticus (SRSE) was introduced by Simon Shorvon in Third London-Innsbruck Colloquium on Status Epilepticus in 2011[17]. SRSE is defined as status epilepticus that continues or recurs 24 h or more after the onset of anesthetic treatment, including those cases that recur on the reduction or withdrawal of anesthesia[15].

1.1.4 *Epidemiology*

The incidence of SE ranges from 20 to 41 per 100 000 per year in large population-based epidemiological studies in USA[18,19]. European studies show somewhat lower overall annual incidence of 10 to 16 per 100 000[20-22]. SE occurs at all ages, but is most common in early childhood and among elderly[19,20,22]. Gender distribution varies in different studies, but appears mostly equal[19]. GCSE is the most common subtype of SE[19], NCSE contributing to 11% of all cases and CSE to 89%[23].
In various retrospective studies 12% to 43% of all SE cases are refractory to treatment and 10% to 15% are super-refractory [15,24-28]. Population based incidence rates of RSE are 3.4 – 5.2/100 000 and those of SRSE 0.7 – 3.0/100 000[29,30].

1.1.5 *Etiology*

Etiologies of SE are numerous[6,31,32]. According to the recent ILAE Task Force on classification of status epilepticus[12], etiologies are divided into Known (i.e. symptomatic) and Unknown (i.e. cryptogenic) categories. This categorization is consistent with the concept of the ILAE Commission for Classification proposal in 2010[33]. Known etiologies are subdivided into categories based on their temporal relationship: acute, remote and progressive. Also SE in defined electroclinical syndromes is notified in one subcategory.
Acute etiologies include acute neurological disorders, such as stroke, head trauma, CNS infections e.g. encephalitis, intracranial hemorrhage or systemic disorders,

such as withdrawal or low levels of AEDs, electrolyte disturbances, abrupt alcohol or drug withdrawal, intoxication, anoxia. Remote symptomatic category includes etiologies that have caused prior insult in the brain (e.g. post-traumatic, post-encephalitic, post-stroke) and progressive category is comprised of progressive neurological disorders (e.g. intracranial tumors, neurodegenerative diseases and PMEs)[12].

Among adults 43-81% of SE episodes occur in patients with previously diagnosed epilepsy[18,19,21,34]. Inappropriate AED treatment is the acute cause of SE in 22% - 34% of the cases[19,24,26,32,35-38]. In patients with previous seizures the percentage might be even higher, up to 53%[38]. Alcohol withdrawal or intoxication is the cause of SE in 8-24% of the cases[19,26,35-38]. Cardiovascular diseases and strokes comprise 4 - 23% of the SE etiologies[19,24,26,35-38]. CNS infections and intracranial tumors account for 4 – 8% [26,35,38] and 4 – 6%[24,26,35,37,38] of the etiologies, respectively. In 4 – 15% of the cases SE results from metabolic disorders[19,26,35,37,38]. The etiology remains unknown for 5 – 15% of the cases[21,26,38]. Among pediatric patients the most common identifiable causes are fever and infection[31,39].

1.1.6 Pathophysiology

Normal epileptic seizures last only for a few minutes[10,11] due to several biological processes that lead to seizure termination. These mechanisms include increased GABAergic drive, neurotransmitter depletion, ATP depletion, ionic changes, acidosis, release of adenosine and peptides[40], and increased activity of pro-seizure processes (breakdown of the blood-brain barrier, inflammation, increased expression of pro-epileptogenic peptides[41,42]). Their failure may promote status epilepticus. Also, failure to increase spatial and temporal synchronization[43] and to cross the critical transition from an ictal to a post-ictal state[44] further induce progression of SE.

A recent review of the pathophysiology of SE pointed out that the whole chain of events in the progression of SE could be seen as a failure of processes that “push” the seizure towards the post-ictal state[45]. Furthermore, the existence of SRSE could be seen as an indicator, that sometimes a stable post-ictal state no longer exists and even after anesthetic treatment the ictal state recurs. Two different processes were proposed to explain this: 1) an ongoing pathological process (e.g.

infection, autoimmune disease) driving brain back to ictal state, 2) underlying pathology or SE itself inducing changes in the brain that make post-ictal state intrinsically unstable[45]. Reinforcing stabilization processes of post-ictal state with AED treatment (i.e. inhibitory GABAergic medication) is necessary to terminate the SE. Most animal models show that experimentally induced SE could be suppressed or terminated with drugs[46].

Animal models have shown that the longer the SE continues, the more difficult it is to treat[47-49]. Experimental evidence suggests that when seizure activity is stimulated for over 30 minutes, the inhibitory mechanisms exhaust and seizure-promoting processes strengthen, leading to self-sustaining SE, although the stimulation has stopped[50,51]. SE seems to activate several growth and transcriptional factors that regulate gene expression of $GABA_A$-receptor in a way pertinent to lowering seizure threshold[52]. Prolongation of SE over 30 minutes induces synaptic $GABA_A$-receptor trafficking and internalization from the cell surface, resulting in loss of inhibition and resistance to pharmacological treatment[49,53,54]. At the same time, NMDA receptor expression increases in excitatory cells amplifying the electric activity[55]. Additionally, expression of pre-synaptic adenosine A1 receptor and GABAb receptor is decreased[50,56]. AMPA receptors lose their GluA2 subunit, which increases calcium permeability and contributes to accumulation of calcium, and possibly leads to neuronal death[57]. Furthermore, aberrant expression of drug transporter proteins may promote increased resistance to AEDs[58].

These modulatory changes in receptor and protein expression are of great importance when considering treatment options for SE, especially refractory SE.

1.2 Outcome

Short-term outcome of SE has been defined in most of the studies based on mortality and functional outcome at hospital discharge or in 30 days. Evaluation of the functional outcome has been performed using clinical scales: Modified Rankin Scale (mRS) and Glasgow Outcome Scale (GOS) or by evaluating the condition relative to baseline prior the episode of SE. The number of studies concerning long-term outcome is low, but those published have evaluated long-term outcome in terms of mortality from one year up to median 12 years[59-62].

1.2.1 Mortality

Short-term mortality rates differ markedly depending on the underlying etiologies, patient's age, refractoriness and seizure duration. Therefore, reported overall mortality ranges from 1,9% to 40%[19-21,28,36,38,63,64]. Mortality has decreased in the 21st century[65,66], possibly due to improved facilities and treatment options. SE with anoxic etiologies is related to high mortality. Anoxia is commonly excluded from SE studies as a devastating entity with poor prognosis and markedly different treatment options and protocols compared to the standard SE treatment protocols.

Long-term mortality rate is markedly higher among SE patients compared to general population. 25% of ICU-treated RSE patients died within one year, despite the relatively low in-hospital mortality of 7.4%[67]. Reported cumulative mortality at 10 years among 30-day survivors after the incident SE episode was 43%[61]. The data on long-term mortality are scarce and indisputable determinants of mortality remain still unclear. Plausible candidates are refractoriness, etiology, pre-existing characteristics of the patient and age.

1.2.2 Morbidity

Status epilepticus bears a considerable risk for increased morbidity after the SE episode[68,69]. Prolonged RSE itself and its treatments may result in general brain atrophy[70], and in neuronal loss and progressive atrophy in the hippocampal area [5,71,72] due to neuronal cell necrosis, gliosis and network reorganizations. Hippocampus seems to be extremely vulnerable to prolonged seizures[73]. Those who survive SE may have cognitive and neurological deficits and increased risk of developing chronic epilepsy[74]. Acute symptomatic SE has a three-fold risk of generating chronic epilepsy when compared to acute symptomatic seizures[74]. Febrile SE (FSE) in children is associated with subsequent temporal lobe epilepsy (TLE) and hippocampal sclerosis[75-78]. This is presumable considering the results from animal studies, in which prolonged hyperthermic seizures of over 60 minutes in immature brain cause TLE[79]. In human patients, the most common long-term complications incorporate chronic epilepsy (20-40%), encephalopathy (6-15%) and neurological deficits (9-11%)[80].

Prolonged hospital admission, acute symptomatic etiology and prolonged seizure are associated with morbidity and decline in GOS at hospital discharge[81]. After ICU-treated RSE 23.8% of the patients were discharged to home, 47.4% to primary healthcare wards and 21% to specialist care facilities[67]. The discharge destination seems to predict long-term outcome, the 1-year mortality being lowest among patients discharged to home[67].

1.2.3 Factors related to outcome

SE is an exceedingly dynamic process and several factors during the process have been proposed to influence the patients' outcome, e.g. etiology, patient's age, depth of coma at onset, structural brain lesion, EEG findings during/after SE and duration of SE[19,25,36,38,61,65,81-83]. Influencing factors can be divided into three categories, 1) patient's pre-existing characteristics, 2) factors related to the current SE episode and 3) treatment and complications. Most of the influencing factors are pre-existing and cannot be affected, therefore, treatment and complications should be in the focus when aiming to improve SE patients' outcome.

1) Patient's pre-existing characteristics

Mortality of SE increases with **age**. Pediatric patients have the lowest mortality rate of 0-5%[6,19,31] and elderly patients have the highest, even up to 76%[61]. In an epidemiologic study from Switzerland, the overall mortality during the hospital admission was 7.6% including all age groups. Mortality among adolescent and adult patients (15-59 years) was 15.4% and among the oldest (>60 years) 53.9%[21]. In the literature, old age, defined in most studies as the age over 65 years, correlates with worse outcome[18,23,32,36,63,81,84-88]. Still, the significance of age may partly be based on pediatric studies, in which age has been the major determinant of prognosis, in contrast to adult SE[65,85]. Higher mortality of elderly SE patients can be related to more frequent appearance of treatment complications and lower compensatory mechanisms[89,90].

The impact of the **gender** on SE's outcome is relatively unclear. Some reports suggest that gender does not have significant effect on outcome[36,84], albeit in some studies female gender seems protective[91,92], and in others even predicts higher mortality[93].

Pre-existing **co-morbidities** are related to the outcome after SE. Multiple medical problems, e.g. diabetes mellitus and extra-cranial malignancy at the onset of SE worsen the prognosis[94,95]. Charlson Comorbidity Index (CCI)[96] is one of the available co-morbidity scores and it is the most reliable score for predicting outcome in various medical problems[97]. CCI is incorporated in Epidemiology-Based Mortality Score in Status Epilepticus - (EMSE) score[98] due to its predictive value for poor outcome and mortality among SE patients[93,98]. Co-morbidities have been estimated to affect the outcome of SE relatively marginally, whereas age and etiology appear more robust and widely applicable predictors[99].

Pre-morbid functional status is related to outcome. Dependence in activities of daily living (ADL) and high mRS score (mRS 4-5) prior to SE are associated with high mortality[67,95,100]. Pre-morbid mRS has been recently incorporated in one of the SE prognostic scores, Modified Status Epilepticus Severity Score (mSTESS)[100]. Although functional capacity prior to SE seems important in relation to prognosis, it has been only rarely reported[95,100-103]. According to these reports, the pre-morbid condition varies substantially between studies, the proportion of patients with poor functional status (mRS 4-5) ranging from 0% to 45%[100,102,103]. This may reflect differences in treatment protocols and patient selection between countries and hospitals, which make comparison of different studies cumbersome.

2) Factors related to the current SE episode

Several studies suggest that underlying **etiology** of SE may the primary determinant of prognosis[89,94,104,106]. Some investigators believe that this might be true especially when SE is treated aggressively, but not necessarily when the treatment has been less than optimal[106].

Previously diagnosed epilepsy has been related to improved survival after SE[19,34,36,92,94,104,107]. The SE episodes in epilepsy-related cases are commonly thought to be easier to treat, and in most studies their outcome is found to be better than that of patients presenting SE with acute symptomatic etiologies[84,92,104]. The presence or absence of previous seizures has been used as a surrogate marker for etiologies (i.e. absence implicating acute symptomatic etiology) in Status Epilepticus Severity Score (STESS)[84]. Low blood levels of antiepileptic drugs (AED) among epileptic patients and inappropriate consumption

of alcohol are related to low mortality[19,32,36], whereas anoxia and acute symptomatic etiologies predict poor outcome and high mortality[23,36,81,91,104,105,107]. Progressive etiologies (e.g. intracranial tumors) and focal neurological symptoms are also associated with poor outcome[87,105]. Also, the finding in the neuroimaging seems to relate to prognosis, so that immaculate imaging findings are associated with better outcome, whereas bilateral abnormalities associate with worse outcome[108,109].

SE type and level of consciousness at SE onset are both incorporated into outcome score STESS because of their relation to the outcome [84,104]. Patients with focal SE are more likely to survive the SE than patients with generalized SE, and coma at SE onset predicts worse outcome than slightly altered or non-altered mental status at onset[104]. Both convulsive SE and non-convulsive comatose SE are related to high mortality[84].

Also, the course of SE, whether it is continuous or intermittent, may affect the outcome. In some studies, continuous SE/seizure activity has been associated with increased mortality[23] and regarded more dangerous than intermittent course[110]. On the other hand in a community-onset pediatric study that CSE cases with an intermittent course had longer SE duration, longer delay in calling the emergency medical service (EMS) and longer delay in arriving at the accident site and emergency department than cases with continuous course, possibly reflecting under-recognition of intermittent CSE as a serious emergency[82]. However, in another pediatric study the initial treatment delay remained equal in both types of SE course[111].

Refractoriness is associated with higher mortality[23,86] and functional deterioration[24,28]. Mortality ranges among non-RSE cases from 8% to 12.6%[25,30,86], whereas among RSE cases it has been reported to be even threefold (16% to 39%)[24,25,27,30,86,113]. Patients' condition after SE at hospital discharge return to baseline in 50% of non-RSE cases, whereas baseline condition is attained only in every third RSE patient[25]. Long-term mortality in SRSE is two times higher than in RSE[29]. Higher mortality among refractory cases treated in ICU might be related to the fact that most deaths among SE patients are caused by ICU complications[94,114].

Duration of SE has been reported to be one of the main predictors of

outcome[23,81,87,89,115]. Differences in defining the duration make the comparison of studies really challenging. Definition regarding the onset of SE seems to vary between studies from the real onset time to the time point of diagnosis[95,116,117]. Also, the exact endpoint of SE is conceptually problematic and varies in the few previous studies that have clearly defined the endpoint. Rantsch et al. defined the end point as the end of the clinical convulsion[90]. However, absence of clinical seizures as the only marker for the cessation of SE seems insufficient, since even 48% of the seizures may continue as electrographic SE[118]. A few studies have used a combination of last clinical seizure and last continuous electrografic seizure as the criteria without any specific time frames[25,104]. Mayer et al. used additional time frame criteria, requiring the patient to be seizure free for at least 72h after the last clinical or electrographic seizure[24]. Return of consciousness or return to baseline mental status is rarely used, but could be the only clinically reliable marker for the end of GCSE. Defining the exact time attributes regarding the duration of SE is of great importance in the future study protocols.

Median duration of SE varies from 2.5 to 48 h in previous studies[24,38,104,119]. Even 25–30 % of the seizures prolong over 24 h [18,21]. In a pediatric study, every minute of ongoing seizure elevated the risk for seizure prolongation over 60 minutes by five percent[82]. Prolonged duration of SE weakens the treatment response[81] and may increase the number of complications due to longer treatment period. Still, even among prolonged refractory SE cases meaningful functional and cognitive recovery is possible[104,120].

Long duration of SE is related to poor outcome[87,89,103,104]. The longer the duration of SE, the worse the prognosis, particularly after 1-2 h of continuous seizures, although the relation may not exist, if the duration exceeds 10 hours[65]. Different predictive duration cut-offs have been proposed in various studies ranging from 30 minutes to several days[23,36,65,86,89,103,121]. This variety might reflect problems in defining the onset and end point of SE, leaving the critical maximum duration undetermined. Nevertheless, permanent brain damage in SE is time dependent, and seizure duration is the only prognostic factor that can be affected by rapid treatment [87].

3) Treatment and complication

Delayed treatment of SE has been associated with poor prognosis[38,86,122] and suboptimal or delayed response to medication[123]. Although there are reports that question the delays' relation to prognosis[84,90,113,124,125], it is evident that prolonged duration of SE associates with poor outcome [87,89,103,104]. While treatment delays correlate with longer duration of SE[111] and treatment protocol adherence improves patients' outcome[116,126,127], delays cannot be ignored in the evaluation of prognostic factors of SE. Treatment of SE consists of several components and delays of those components and their effect on prognosis of SE is addressed more detailed in the Delays in the treatment-section later in this chapter.

Adherence to treatment protocols, quality of treatment, proper drug sequence and management within the suggested timeframes seem to have a significant impact on the prognosis of SE. Existing literature and experts' opinions strongly emphasize the importance of the quality of treatment[116,126-129], although a recently published study suggested that treatment latency and adherence to protocol are not related to outcome of SE[130]. Additionally, delayed third-line treatment >1 day has been associated with increased recovery compared to delay <1 day[131]. This discrepancy may reflect the finding that delays in the treatment and compliance with suggested protocols are far from optimal, regarding both adults and children[34,111,116]. Also, heterogeneity of etiologies, SE severity and refractoriness may complicate the interpretation of the results.

Evidence of the significance of **intravenous anesthetic drug (IVAD)-treatment** itself on the prognosis is contradictory; some studies consider it harmful for the patients[117,132,133], while opposite conclusions suggest that the poor prognosis of IVAD treated patients is associated rather with more severe etiology of SE, refractoriness and increased number of complications, than with IVAD treatment itself[100,103,134-136]. Anaesthetic treatment is discussed more detailed in Treatment section later in this chapter.

Systemic **complications** in the treatment of SE are commonly encountered and even 85% of the SE patients present failure of at least one organ system during the SE episode[23]. Complications may involve every organ system. Risk of complications increases due to prolongation of SE and treatment in ICU[38,81,137,138]. Conversely,

complications increase the risk of refractoriness[137] and prolong hospitalization[95]. A few studies report that mortality in SE might be related to systemic complications even in 12 - 50% of the cases[23,100,101,138]. Complications, such as infection[102,103,137], cardiac injury, arrhythmias, vasopressor use[101,102,132,139,140] and mechanical ventilation[102,132], have been associated with mortality and poor outcome. In the latest Colloquium on status epilepticus in Salzburg 2017 a tool to estimate the total burden of complications was introduced. The study suggested that complications in more than 3 organ systems during the course of SE were related to mortality and poor functional outcome[141].

1.2.4 Outcome scores

During the last decade four outcome scores have emerged: STESS[84,88], mSTESS[100], EMSE[98] and END-IT[109]. These scores include variables that are related to outcome (Table 1.-4.). STESS and EMSE have been internally and externally validated. Most of the above-mentioned variables associated with prognosis are incorporated in the scores, however none of the scores take into account delays in the treatment, nor the duration of SE.

Table 1. Outcome scores of SE: STESS

STESS		
RELATIVE FACTOR	**CATEGORIES**	**POINTS**
Consciousness	Alert or somnolent/confused	0
	Stuporous or comatose	1
Worst seizure type	Simple-/complex-partial, absence, myoclonic	0
	Generalized-convulsive	1
	Non-convulsive in coma	2
Age	< 65 years	0
	≥ 65 years	2
History of previous seizures	Yes	0
	No or unknown	1
TOTAL		**0-6**

Table 2. Outcome scores of SE: mSTESS

mSTESS		
RELATIVE FACTOR	**CATEGORIES**	**POINTS**
Consciousness	Alert or somnolent/confused	0
	Stuporous or comatose	1
Worst seizure type	Simple-/complex-partial, absence, myoclonic	0
	Generalized-convulsive	1
	Non-convulsive in coma	2
Age	< 65 years	0
	≥ 65 years	2
History of previous seizures	Yes	0
	No or unknown	1
mRS	0	0
	1-3	1
	≥ 4	2
TOTAL		**0-8**

Table 3. Outcome scores of SE: EMSE

EMSE		
RELATIVE FACTOR	**CATEGORIES**	**POINTS**
Etiology	CNS-anomalies	2
	Drug reduction/withdrawal/poor compliance	2
	Multiple sclerosis	5
	Remote cerebrovascular disease, brain injury	7
	Hydrocephalus	8
	Alcohol abuse	10
	Drug overdose	11
	Head trauma	12
	Cryptogenic	12
	Brain tumor	16
	Metabolic:sodium imbalance	17
	Metabolic disorders	22
	Acute cerebrovascular disease	26
	CNS-infection:acute	33
	Anoxia	65
Co-morbidity	MI, CHF, PVD, CVD, dementia, CPD, CTD, Ulcer, mild liver disease, DM	10
	Hemiplegia, moderate/severe renal disease, Dm with organ failure, any tumor	20
	Moderate or severe liver disease	30
	Metastatic solid tumor, AIDS	60
Age	21-30	1
	31-40	2
	41-50	3
	51-60	5
	61-70	7
	71-80	8
	>80	10
EEG	no LPDs, GPDs or ASIDs	0
	GPDs	40
	LPDs	40
	ASIDs	40
	BS (spontaneous)	60
TOTAL		**13-195**

Table 4. Outcome scores of SE: END-IT

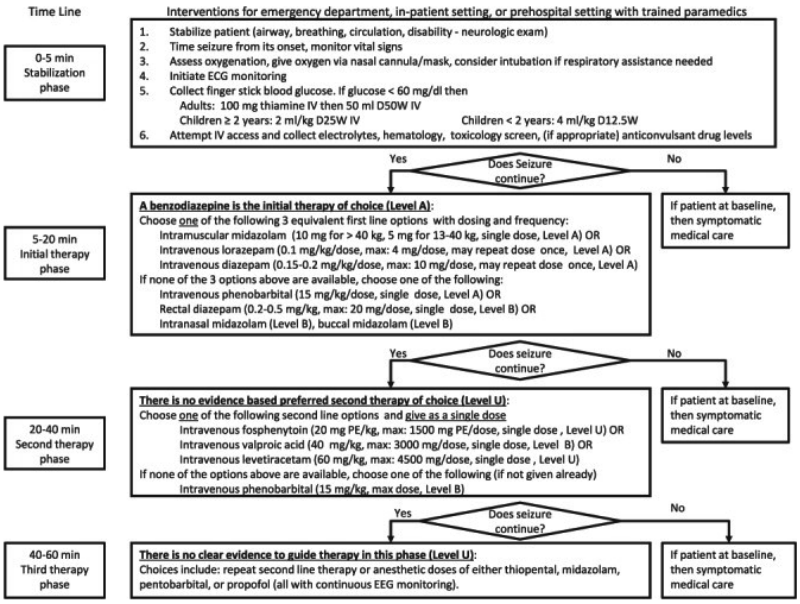
END-IT		
RELATIVE FACTOR	**CATEGORIES**	**POINTS**
Encephalitis	Yes	1
	No	0
NCSE	Yes	1
	No	0
Diazepam resistance	Yes	1
	No	0
Image	Bilateral lesions/ diffuse cerebral edema	2
	Unilateral lesions	1
	No responsible lesion	0
Tracheal intubation	Yes	1
	No	0
TOTAL		**0-6**

STESS is a tool for systematic evaluation of the outcome of SE patients and may be used to recognize patients, who need aggressive treatment[84,88]. In the original study, STESS points 0-2 and 3-6 predicted good and poor outcome, respectively. However, the cutoff-point for poor outcome is a subject of debate[62,90,142,143,144]. mSTESS is a modification of the original STESS incorporating evaluation of pre-morbid condition. mSTESS >4 predicts fatal outcome with overall accuracy considerably higher than that of STESS≥3[100]. EMSE is an explorative, hypothesis generated, epidemiology-based score, where score points for each parameter were derived from previously published mortality rates. EMSE, with cut-off 64 points, yielded the best results in predicting mortality. Studies comparing STESS and EMSE have shown some superiority of EMSE in predicting mortality and functional outcome[145], however EMSE may lack utility in the emergency room in the early phases of SE treatment. END-IT was created in China, and the baseline population differed markedly from the Western population in age distribution and in etiologies. Consequently, it might not be directly applicable in Western countries[109].

1.3 Treatment

1.3.1 Treatment guidelines and protocols

The first international guideline of the management of convulsive SE was published in 1993[6]. It was consensus-based and provided physicians with consistent and rational approach. During the last decade a few updated guidelines have emerged aiming to provide an evidence-based guideline[146-148]. Protocols facilitating urgent treatment have been supported by experts[149,150]. The latest update was published in 2016, focusing on convulsive SE in adults and children[151]. The guideline proposed an updated treatment algorithm for convulsive SE, based on Level A and B evidence concerning the recommended medication in the early stages of SE. Recommendations for the treatment of RSE or SRSE have been addressed in the earlier guidelines and reviews[15,147,148].



Proposed treatment algorithm for status epilepticus.

Fig 1. Proposed treatment algorithm for status epilepticus.
Reprint permission from AES.

Staged treatment approach has been recommended since the first guideline in 1993[6,146,147,149,152], but the increased understanding of the pathophysiology has led us to recognize that "time is brain" also in SE, although there is no evidence-based timeframe for treatment. Current guidelines suggest aggressive early treatment with the tendency towards shortening the recommended timeframes of treatment[15,147,148,151].

Treatment of SE is an extremely dynamic process with diagnostic challenges, several treatment stages, and potential misinterpretations over the whole management process. Therefore, streamlining the treatment protocol is needed. Although treatment of acute stroke is more straightforward than that of SE, approaches used in stroke treatment chain streamlining could be implemented to optimize the SE management. Changes in the management protocol, after evaluation of the crucial delays in the treatment chain of stroke thrombolysis candidates, have reduced the intra-hospital delay (door-to-needle-time) from median 105 minutes to 20 minutes[153].

1.3.2 Treatment

Staged treatment protocols guide the treatment in the early phases of SE, while there are no evidence-based guidelines for the treatment of RSE and SRSE. Treatment of RSE is based on anesthetic treatment and is covered as the third-stage treatment section in this literature review. Treatment of SRSE leans on experts' opinions, and anesthetics (propofol, barbiturates, midazolam, ketamine, inhalation anesthetics) with up to 3 different AEDs in large doses are recommended. Treatment of the etiology of SRSE is important and therefore also immunotherapies (high dose prednisolone, iv. immunoglobuline, cyclophosphamide, rituximab), magnesium-infusions, hypothermia, ketogenic diet and stimulators (VNS, DBS) should be considered[15,45,154]. Newest treatment approaches include neurosteroids (extrasynaptic GABAa receptor inhibition)[155-157], NMDA inhibitors and calcineurin antagonists[158,159].

1.3.3 Delays in the treatment

No systematic studies on the delays in the clinical course of SE have been published prior or during this study. Most of the studies regarding delays in the

treatment of SE concentrate on treatment delay, which reflects a limited part of the whole process. Comprehensive evaluation of the management process requires recognition and assessment of all individual delay components.

Treatment delays

A recent review of the treatment delays and treatment adherence in SE found only 17 publications considering treatment delays since year 2000, two of which are part of this thesis. All of them issued delays to initial treatment, but only five publications issued delays to second- and third-stage medications[160]. This review demonstrated pervasive delays in the treatment of SE.

The effect of treatment delay on outcome in SE is controversial and subject to debate. Most studies, as seen in the recent review[160], have focused only on the relation between first-stage medication and outcome. Several studies show that the treatment delay has a clear impact on the prognosis; the longer the delay, the worse the outcome[38,86,122,161], and some suggest that, besides the etiology, the treatment delay plays an important role[89,162,163]. Opposite results suggest that a long treatment delay does not correlate with increased mortality[84,90,94,125], and consequently the prognosis of SE is mainly determined by its biological background[113] and affected by its refractoriness[90]. It is also possible that treatment delay is critical for extremely severe SE episodes, although not for all types of SE[125]. Clarification of this matter is warranted.

1) First-stage treatment

There are several requirements for the effective first-stage treatment.

The most **effective medication** should be used. Intravenous benzodiazepines (lorazepam, diazepam, clonazepam), intramuscular midazolam and rectal diazepam are approved as efficacious and essentially equivalent first-stage medications with clear superiority to placebo[162,164-167]. Earlier, rectal diazepam gel has been used as an alternative for intravenous administration and usage in pre-hospital environment, e.g. at home, has been advised as a measure to shorten the treatment delay[168]. Development of preparations for other administration routes (buccal, intranasal, intramuscular) has enabled more rapid and socially more

acceptable administration of medications[164,167]. Especially after RAMPART study[162], the usage of intramuscular midazolam has increased[169]. Although a few studies on North American patients report that non-benzodiazepine initial therapy was applied in only up to 7% of convulsion cases[127,170], a worldwide survey reports a substantially higher proportion of 67%[131].

Adequate dosing of the medications is essential. Under-dosing benzodiazepines might be falsely interpreted as benzodiazepine-resistant SE and may lead to unnecessary acceleration of the treatment to higher stages[171]. Over-treatment with benzodiazepines has been associated with increased need for intubation and prolonged hospital stay[172]. 22% - 90% of the patients have been reported to receive suboptimal weight-based dosing[76,170,173,174]. Pre-filled medication dispensers might be influential for adequate dosing during the initial treatment. Overall pre-hospital benzodiazepine medication has been considered safe and efficient with the benefit of the treatment exceeding the risks of complications, such as respiratory depression[82,116,165,175,176].

The medication should be **administered without delay**. Although the suggested timeframe is not evidence-based, administration should take place within 5 - 10 minutes after seizure onset[148,151,177,178]. It has even been suggested that rapid administration per se is probably more important than the actual agent[179]. Adherence to initial treatment protocol has been reported to be the main factor associated with seizure termination[116]. Regardless of this, reported median treatment delays are far from optimal and range from 28 minutes to several hours[38,76,86,90,111,116,123,129,161,168] among public onset SE cases. Only ICU onset cases have managed to meet the treatment delay requirements[23] so that initial treatment delay in cases occurring in hospital is shorter than the of out-of-hospital onset cases[111,126,128]. In addition, only 31%-54% of the patients are initially treated out-of-hospital[76,111,161,170], albeit pre-hospital treatment, especially pre-hospital diazepam among pediatric patients, has been associated with shorter duration of SE[116,175] and pre-hospitally applied rectal medication lowers the incidence of prolonged convulsion[82]. Patient education and a clear seizure emergency plan are needed to reduce unnecessary delays[168].

It is crucial to interpret the **response to medication** correctly to be able to continue with the adequate treatment in the initially treatment-resistant cases with a high

risk of nascent SE. Caregivers treating patients with recurrent seizures should be advised to monitor the clinical response in order to recognize the need for immediate professional evaluation [181].

2) Second-stage treatment

Traditionally available intravenous medications are phosphenytoin and valproate and newer ones include levetiracetam and lacosamide. Proper evidence of any agents' superiority is lacking[182-185]. Two studies propose that valproate and phosphenytoin are equal in efficacy[185,186]. In a few studies, phosphenytoin has been combined with traditional first-stage medication in out-of-hospital treatment[116,187] and the combination might be efficient in 2/3 of the seizures[122]. Still, safety and storage issues of phosphenytoin restrict its use on site. There is some evidence that the use of newer AEDs in the treatment of SE may lower the chance of return to baseline condition at discharge and result in higher rate of refractoriness[188,189], but a newly published randomized study suggested that levetiracetam controls status epilepticus with an efficacy comparable to that of phenytoin[190]. Therefore, there is an urgent need for the results from an ongoing randomized trial comparing phosphenytoin, valproate and levetiracetam in the treatment of established SE, ESETT[191] and from the planned randomized pediatric trials ConSEPT and EcLIPSE comparing levetiracetam and phenytoin[192,193]. It is worth noting that in ESETT, patients are randomized according to the drug, but the delay in giving the agent is uncontrolled.

Only a few studies report onset-to-second-stage medication delay. In those studies, median delay ranges from 69 to 105 minutes[111,116]. This is clearly longer than the guidelines' suggestions to move to second-stage medication within 20 - 40 minutes, if seizures persist after first-stage treatment[148,151,177,178]. Adherence to protocol and attempts to reduce delays is important, since in a prospective study[116] patients receiving first long-acting AED according to the treatment protocol (fosphenytoin or lorazepam) were 19.9 times more likely to obtain seizure termination.

3) Anesthesia i.e. third-stage treatment

According to the guidelines, the third-stage treatment, i.e. intravenous anesthetic drug (IVAD), includes treatment with propofol, thiopental (in USA rather pentobarbital) and/or midazolam[147,148]. Additionally, the use of ketamine is increasing. So far there are no studies showing superiority of any of the IVADs used, and the choice of agent does not seem to influence the outcome or mortality[25,115,194]. Using propofol bears a 10 % risk of life-threatening complication of propofol infusion syndrome (PRIS)[195]. On the other hand, propofol shortens the hospital stay and may improve the patient outcome, as compared with other anesthetics, possibly due to the short duration of action[25]. However, propofol does not significantly differ from other agents[34,196], since all IVADs may induce serious adverse reactions, mainly hypotension and respiratory depression[134].

Treatment with IVADs is suggested to be monitored by EEG to demonstrate seizure suppression, or burst-suppression (BS) as the proper treatment response, but also suppression of all background activity has been proposed[148,197]. BS is suggested in the European guidelines[147], while the American guideline states that EEG endpoint of treatment is controversial[148]. The evidence for the utility of BS as a treatment goal is scarce and the effect of BS on prognosis remains undetermined[65]. BS level has been advocated as the goal for SE treatment based on evidence, that the depth of EEG suppression (i.e. BS) correlates with favorable treatment response[115,198]. Still, its significance in predicting permanent absence of seizures, mortality, or clinical recovery has been questioned[25,115,198]. In a few studies the achievement of BS was not superior to epileptiform suppression with regard to mortality or functional outcome[25,199]. In turn, presence of BS, regardless of SE etiology or the medication administered, has been associated with grave prognosis[85] and seizure control without suppression of electric activity to BS or isoelectric level is associated with good functional recovery[102].

Initiation of IVAD treatment in cases refractory to first- and second-stage treatment is recommended after 30 - 70 minutes of continuous seizure activity, especially in GCSE cases[148,151,177,178]. Reports on the delays in IVAD initiation and the effect of the delays on the outcome are nearly lacking. In a pediatric study, median delay in starting anesthesia was 180 min[111] and in an adult study from

years 2001-2010, onset-to-anesthesia-delay was reported to be 1–2 h in 37 % of the cases and 2–24 h in 63 % of the cases[34]. Recent results from a global audit (2015), where only 16% of the patients are treated within 1 hour, show no real improvement[131]. It has been claimed that long delay in starting anaesthesia does not necessarily mean poor outcome[94], but the evidence is scarce and requires further studies in the future.

Maintenance of BS for at least 24 hours is recommended by the guideline[147]. This policy is well adapted, since circa 70% of the treating physicians aim at BS level for 24-48 hours[180], although there are no data indicating the duration of treatment sufficient to obtain permanent seizure termination[148]. In previous reports, the total anaesthesia time varies from median 21.5 hours to several days, depending on the severity and refractoriness of the SE[34,102,112]. The length of IVAD treatment is a subject of debate. Long anesthetic treatment has been associated with both poor[102] and good[94] outcome. It predisposes to increasing number of complications as the sedation time prolongs and in that way poor outcome may be in prospect. Also, sedation in general, especially in higher doses seems to be associated with a higher incidence of cognitive dysfunction[200]. However, multiple studies have shown that in etiologies other than anoxia the possibility of meaningful functional and cognitive recovery even after weeks of anesthetic treatment is possible. No clear duration of SE or number of failures in weaning the anesthetics can be defined to justify the case to be considered futile[87,102,104,120,201].

Pre-hospital delays

Pre-hospital management of SE has been studied mainly with the focus on medication selection, safety, and efficacy of the treatment given out-of-hospital[82,116,165,175,176]. Other aspects in the pre-hospital period have raised less interest. Although there is no clear evidence of the effect of the delay in pre-hospital initial treatment on patients outcome[161], lack of pre-hospital treatment has been associated with prolongation of SE over 60 min among pediatric patients[82]. As mentioned above, administration of AEDs already out-of-hospital concerns only a minority of SE patients and therefore pre-hospital period could be seen as a missed opportunity for timely intervention, as speculated in a recent review[160].

Delays in **calling the ambulance** and factors related to those delays have not been systematically studied among SE patients. Reported delays from onset to alarm are 12.5 to 30 minutes[76,161], which are somewhat shorter than reported median delays among stroke-patients[202,203]. Comparison is inadequate, since reports on delays among SE patients are so scarce. Long delays in medical emergencies reflect wait-and-see-attitude among patients and caregivers, what seems to be difficult to change despite public education campaigns on emergencies like stroke[203]. Among stroke patients fear of disease and hospital and living alone were the main factors lengthening the alarm delay, whereas severe symptoms and moderate to high score (> 8) on NIH Stroke Scale (NIHSS) at onset, presence of family members or bystanders and female gender were associated with shorter delays[202-204]. Among SE patients, continuous convulsive seizures in SE could be comparable to high NIHSS-score in stroke as a marker for severity leading to accelerated operation. Indeed, this was seen in a pediatric study, where intermittent seizures triggered alarm call with longer delay than continuous seizures[82].

Reports on **pre-hospital delay** range from 30 minutes to 105 minutes among SE cases[24,76,82,161,173,206,207]. In a pediatric study on community-onset SE, intermittent course of SE onset was associated with longer delay in arriving at the accident site and emergency department than that in cases with continuous course, reflecting under-recognition of intermittent CSE[82]. Knowledge of other relating factors among SE patients is deficient. Stroke studies divide pre-hospital period to sections: onset-to-call time, on-scene time (OST) and transportation-to-hospital time. Onset-to-call time may account even for 20% of the total pre-hospital delay[203] and delays depending on the patient were estimated to be the most significant ones[208]. Minimization of the OST is important especially in maladies, for which treatment is available only in hospital, e.g. thrombolysis in acute stroke. OST could be reduced by 10 % by EMS personnel in a prospective interventional study of stroke patients. Level of expertise of the ambulance crew seems essential for the OST, since higher expertise level decreases the need to consult physician via phone and consequently reduces OST[209]. However, increase in the number of personnel available on site did not markedly change OST[210]. Acute myocardial infarction studies show that the importance of the length of OST and the time spent on transportation decreases, if the treatment could have been started on site immediately after diagnostic procedures and managed through telemedicine consultation[211]. This approach could apply on SE patients. The most important

factors in stroke and cardiac infarction studies relating to pre-hospital delays constitute of early diagnosis on site[210,212], usage of stroke as the specific dispatch code (in stroke studies) and triaging patients to highest priority[203,208]. In reducing pre-hospital delays, multiple strategies should be considered including education, symptom detection and prediction systems, pre-notification of hospital, physician staffed EMS units, telemedicine consultation and triaging patients directly to specialized hospitals[202,215].

Organization of EMS systems and treatment arrangements in hospital districts vary tremendously throughout the world and even within countries. There are very little, if any, studies comparing different systems and their effect on SE patients' outcomes. Patients treated in urban versus rural area hospitals were compared relative to mortality, with significantly higher mortality in urban areas, where also the quality of global drug treatment was inferior[126]. Furthermore, a trend towards worse outcome in tertiary hospitals was found in a prospective cohort comparing outcome in patients treated in tertiary hospital versus regional hospital, although groups were equal in relation to age and SE severity (STESS)[213]. However, stroke patients gained benefit of being transported directly to adequately specialized hospital with a stroke-unit rather than to other, possibly nearest, lower-level hospital[214].

Diagnostic delays

Early recognition of SE and a proper diagnosis without delay are of greatest importance. Missed or delayed diagnosis is associated with a higher likelihood of poor response to treatment and worse outcome[176]. Median diagnostic delay has been reported to be 45 minutes to 4 days[95,116], the shortest delay consisting only of patients with GCSE in France, where emergency units routinely include a medical doctor[116]. The delays in different EMS settings and in other types of SE might be even longer. In a recent study, the diagnosis of NCSE was missed by EMS in over 60% of the cases, whereas CSE was recognized in all cases expect for those with transformation into subtle SE[216]. These findings call for rigorous education on the risks of SE and support the conclusion presented in previous studies that there is a need for simplified criteria for suspicion of an imminent SE[116,168]. This approach is supported by studies on cardiac infarction, demonstrating that pre-hospital diagnosis shortens the pre-hospital delay and reduces mortality[211,212].

Availability of EEG is essential for diagnosis, especially among NCSE cases. In ICU only 20% of SE diagnosis were made before EEG[217]. Median delays in starting continuous EEG (cEEG)-recordings range from 195 min (from SE onset) to 16.7 hours (from ICU admission)[116,218]. Delays in initiation of cEEG in cases with electrographic SE has been associated with high mortality[218]. Improved availability of EEG is warranted, and several alternative settings have been tested. Forehead EEG electrode set shows a sensitivity of 50% in detecting NCSE with no false positive cases[219]. A 5-minute eEEG recording was shown to expedite SE diagnosis without compromising reliability in ED[220] and a 7-electrode montage led to quick and reliable seizure detection in ICU[221]. In the future, seizure detection, seizure prediction and closed-loop warning systems could be useful for epilepsy patients in better recognition of SE[222]. Availability of EEG in ambulance for diagnosing purposes would be comparable to ECG for diagnosing AMI and mobile CT-imaging units for diagnosing stroke[202].

Treatment response delays

Evaluation of the treatment response has been performed mainly for duration of SE. As mentioned above, that parameter lacks uniform definition and therefore stepwise evaluation of the treatment response is advocated.

End of the first seizure in SE period has been reported to occur 60–180 min after the SE onset[23,116]. The median delay from SE onset to the end of the last seizure i.e. **clinical seizure freedom** has been reported to be 2.4 h in non-RSE and 92 h in RSE cases[27]. Only two prospective studies have issued the delay from SE onset to BS. The median delay of **BS** with thiopental anesthesia was 11.5 h[223], and the corresponding delay with propofol anesthesia was 6 h[224]. The effect of the BS delay on prognosis is unclear, but one study speculates that achievement of BS during the first 7 days during the SE treatment is associated with better prognosis of patients with prolonged refractory SE in one-year follow-up. The reason for this might be related to better treatment strategies with patients achieving BS or to a greater treatment resistance of patients not achieving BS[101]. No previous studies have reported on the delay in **return of consciousness.** However, the delay from onset to clinical recovery has been associated with mortality after 10 hours[104].

2 AIMS OF THE STUDY

1) To define and determine the length of delay components in the treatment of status epilepticus. (I)

2) To detect the most important factors related to pre-hospital delays in the treatment. (II)

3) To determine the delays and factors related to the duration of status epilepticus. (III)

4) To study the effect of the delays in the treatment on the outcome of the patients at hospital discharge. (IV)

5) To find the most important delay components in the treatment chain for status epilepticus treatment protocol streamlining. (I-IV)

3 MATERIAL AND METHODS

3.1 Study design

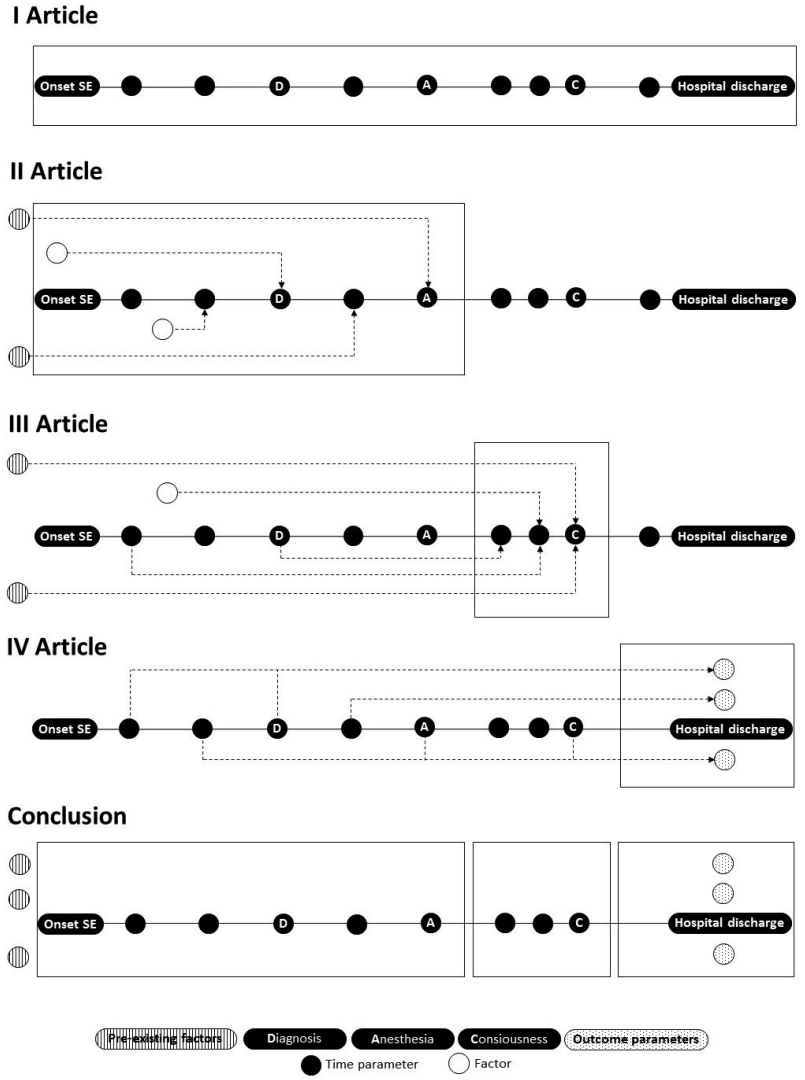


Fig 2. Structure of thesis.

This study consists of four parts, all examining the same retrospective patient cohort from Helsinki University Central Hospital (HUCH). The study material includes consecutive adult patients (over 16 years of age) diagnosed with SE (I-II) or with generalized convulsive SE (GCSE) (III-IV) and treated in the HUCH ED over a two-year-period from January 2002 till December 2003. The first two publications (I-II) comprise all types of SE. Since SE patients are a very heterogeneous group, the last two publications (III-IV) exclusively examine CGSE patients, which is the largest subgroup of SE patients.

HUCH is a tertiary hospital in Southern Finland serving a population of 1.4 million. Emergency service in the hospital district is provided by one tertiary university hospital (HUCH) with neurological emergency service operating round the clock, seven regional hospitals, in which the ED is run by internists, neurological consultation being available during office hours, and several primary health care centres. The EMS system includes paramedic-, nurse-, and physician-based EMS units in either ambulance or helicopter. At the time of material collection second-stage medication was not at disposal for EMS. In cases of benzodiazepine resistant SE, physician- and nurse-based EMS units may induce anesthesia and intubate the patient at emergency site, based on consultation of the physician on shift. Emergency calls are centralized in Finland and trained personnel selects the type of unit needed at emergency site. Physician – or nurse-based units are recruited in cases of suspected SE, whenever available. All rescue units in the HUCH area have been instructed to transport SE patients, independent in daily living, primarily to HUCH ED.

3.2 Collection of material

The patients were identified in the HUCH electronic patient database by the ICD-10 code G41 (SE), either as a primary or a secondary ED discharge diagnosis, yielding a total of 87 patients. Patients not meeting the criteria of SE (I-II) or the criteria of GCSE (III-IV) were excluded from the analysis, despite having the SE or GCSE diagnosis in their records. This resulted in a total yield of 82 SE patients and 70 GCSE patients.

The data were collected from the original medical records on a preformatted standard form designed for this study. The records consisted of notes made by

nurses and doctors of EMS, health care centres, regional hospitals, HUCH ED, ICU or neurological ward. Ambiguous data were evaluated by the research team to obtain consensus on conflicting remarks. If the consensus concerning the original coding rules changed, the data in question were recollected and re-evaluated for all cases. The electronic database was created using MS Access for data recording. The patient identification information was removed before further analyses. Most of the data concerning the grouping variables were objective, however, the definitive patients' group assignments were settled after the data collection.

This study conforms to the Finnish legislation concerning medical research and the permission was granted by the HUCH Department of Neurology.

3.3 SE definitions

In this study established SE was defined as continuous seizures lasting over 30 minutes, or as several recurrent seizures without returning consciousness, or occurrence of more than four seizures within any one hour irrespective of return of consciousness in between. The definition was based on the national and local guidelines and followed the operational definition of SE being used at the time of material collection. The present-day definition was still under preparation at that time.

Patients having a convulsive seizure at any point of the SE period were considered as having CSE. Seizures with impaired consciousness, either primarily or secondarily, were considered as GSE and those with normal consciousness were considered as focal SE. Seizures lacking motor manifestations were considered as NCSE. The seizure description of individual patients was collected from original medical records and seizure classification was also based on EEG, when available.

The onset of SE was defined as the beginning of the first seizure fulfilling the above-mentioned criteria for established SE or GCSE. No clear definition for the end of SE was found in the literature. Therefore, we applied a stepwise definition for cessation of SE or GCSE applying three separate parameters: BS, clinical seizure freedom and return of consciousness. BS refers to the beginning of the first BS sequence during the current episode. Clinical seizure freedom refers to the end of

the last clinical signs of seizure, and return of consciousness refers to the time point, when the patient could communicate meaningfully.

Patients failing to respond to the first- or second- stage treatment were considered as having RSE. SE continuing or recurring 24 h or more after the onset of anesthesia was considered as SRSE.

3.4 Validation of the study material

The retrospective character of the material raised the need to evaluate the documentation of the time points for accuracy and availability.

The data on delays were based on events with exact time points documented in the medical records, whenever possible. For events not accurately documented, clinically grounded estimation of the event time was based on time frames with exact documented time points at each end.

For accuracy evaluation we developed an accuracy score (L_{WAS}) based on a mathematical formula for weighted average. L_{WAS} for each time parameter was calculated using the formula

$$L_{WAS} = \frac{\sum_{i,j,k=1}^{3} k(x_i + y_j)}{\sum_{i,j=1}^{3} (x_i + y_j)}$$

where: k = accuracy coefficient (1, 2, 3). x_i = number of cases at the beginning of the time interval in question with accuracy coefficient i. y_j = number of cases at the end of the time interval in question with accuracy coefficient j.

L_{WAS} ranges from 1 to 3. Score 1 indicates exact time in documentation, whereas scores 1–2 and 2–3 indicate accuracy of 0–5 or 5–30 min, respectively. Inaccurate time points were excluded from the analyses. L_{WAS} refers to the deviation of the time parameters from the absolute accuracy in the medical records.

For the availability of the delay material included in the final analysis, we calculated Data availability (DA), which refers to the percentage of cases for which any data was available.

In addition to inaccurate time points, missing events, e.g. no anesthesia, events happening during pre-status period, or events with unknown data were excluded from the final analysis. Detailed reasons for missing values were reported in each publication.

3.5 Measures

3.5.1 Delay parameters

We determined and calculated several delay parameters. Delays in the treatment consisted of pre-hospital delays, diagnostic delays and treatment delays. Treatment response delays consisted of the length of the first seizure, delays in obtaining burst-suppression, achieving clinical seizure freedom and returning of consciousness. The three latter delay parameters denoting markers for cessation of SE. Periods in the treatment, such as HUCH admission were calculated. Various diagnostic procedures, treatment interventions or other relevant events documented in the medical records were also recorded. Delay parameters are presented in Table 5.

Table 5. Delay parameters used in studies I-IV.

DELAYS IN THE TREATMENT	STUDY	STUDY	STUDY	STUDY
PRE-HOSPITAL DELAYS	**I**	**II**	**III**	**IV**
Onset-to-alarm	x	x	x	
Standard ambulance	x			
Physician staffed rescue unit	x			
Alarm-to-EMS	x			
Standard ambulance	x			
Physician staffed rescue unit	x			
Onset-to-first-ED	x	x	x	
EMS-arrival-to-first-ED	x			
Onset-to-tertiary-hospital (HUCH)	x	x	x	x
DIAGNOSTIC DELAYS				
Onset-to-diagnosis	x	x	x	x
Clinical diagnosis	x			
Diagnosis based on EEG	x			
Onset-to-EEG	x		x	
Diagnostic EEG	x			
Treatment response EEG	x			
Onset-to-EEG-monitoring	x		x	
HUCH-ED-to-cEEG	x			
Anesthesia-to-cEEG	x			
HUCH-ED-to-etiological-investigation	x			
CT of the head	x			
MRI of the head	x			
Lumbar puncture	x			
Sign. laboratory finding	x			
TREATMENT DELAYS				
Onset-to-initial-treatment	x	x	x	x
Onset-to-second-stage-medication	x		x	x
Onset-to-anesthesia	x	x	x	x
TREATMENT RESPONSE DELAYS				
Onset-to-first-convulsion-end	x		x	
Onset-to-Burst-suppression	x		x	x
Anesthesia -to-BS	x			
Duration of first BS	x			
Onset-to-seizure-freedom	x		x	x
RSE/SRSE cases	x			
Non-RSE cases	x			
Total-convulsion-time (convulsive cases)	x			
Onset-to-consciousness	x		x	x
Non-RSE cases	x			
PERIODS IN THE TREATMENT				
Pre-status-period	x			
Total-ICU-time	x			x
Total-anesthesia-time	x			x
HUCH-treatment-period	x			

Delay parameters were counted from the onset of SE/GCSE, if not stated otherwise. "Total time" (e.g. anesthesia) was calculated by adding up the length of each individual event (e.g. anesthesia sequence) during the SE period. "Period" was calculated from the onset till the end of the event despite interruptions in between.

Onset-to-alarm refers to the primary alarm, i.e. the delay in calling the ambulance. In some cases several ambulance calls were made, but only the primary contact was calculated. The term First ED denotes to the ED in which the patient was treated for the first time during the SE/GCSE. Only the cases transported to the ED by EMS were calculated to the Onset-to-first-ED time. HUCH ED was exclusively considered as the Tertiary Hospital ED, and all other ED's, regardless of the level or location were collectively grouped as other hospital ED.

Initial treatment was defined as the first AED given, which was not necessarily first-stage medication. First-stage medication included iv. or rectal diazepam or iv. lorazepam. The patient was considered to respond to the initial treatment, if the seizure stopped within 10 min after iv. administration or 20 min after rectal administration of the initial medication, with no other simultaneous medications. The second-stage medication was defined as first second-stage medication given, which included iv. phosphenytoin or valproate. The patient was considered to respond to the second-stage-medication, if SE resolved after second-stage-medication without anaesthesia. The third-stage medication included anaesthesia with propofol, thiopental or midazolam and the start of the third-stage medication was defined as the time point of induction of anaesthesia (onset-to-anaesthesia).

Seizures occurring no more than 48 h prior to SE onset and reported as relevant part of the process are referred to as the pre-status period. Onset-to-first-convulsion-end refers to the time between the onset of GCSE and the end of the first clinical convulsion.

3.5.2 Other parameters

Parameters for grouping variables were defined in three categories: SE type-related, patient-related, and SE episode-related. The parameters and their use in different publications are presented in Table 6. Considering the goal of the pre-

hospital part of this thesis (II), the precondition for variables used in that publication was that they could be determined for each case based on the period before the patient was admitted to hospital, i.e., either unambiguous background information, visible clinical signs of epileptic seizure, or documented pre-hospital events.

Seizures lasting clinically at least 30 min were defined continuous. All other types of seizures were considered intermittent. Only subjects with previously diagnosed epilepsy were considered as patients having epilepsy. For age as a grouping variable, 65 years was selected as the classification basis. Healthcare units included hospital EDs, in-patient departments in hospitals and healthcare centres, as well as nursing homes. Events occurring prior to the first ED were considered as pre-hospital events. STESS (A16) was used for SE severity assessment.

Table 6. Grouping variables used in studies II-IV.

PARAMETERS		STUDY II	STUDY III	STUDY IV
SE TYPE RELATED				
SE type 1	CSE	x	x	x
	NCSE			
SE type 2	GSE	x	x	x
	Focal			
Pre-status period	Yes	x	x	
	No			
SE onset	Continuous	x	x	
	Intermittent			
PATIENT RELATED				
Epilepsy	Yes	x	x	
	No			
Age under 65	Yes	x	x	
	No			
Living	Home	x		
	Home with someone else			
	Nursing home			
SE EPISODE RELATED				
Scene at SE onset	Home	x		
	Healthcare unit			
	Public place			
SE onset at home, pt living alone	Yes	x		
	No			
Initial treatment before EMS	Yes	x		
	No			
Rectiol as initial treatment	Yes	x		
	No			
Effect of the initial treatment	Yes	x	x	
	No			
	Spontaneous cessation			
First ED	Tertiary hospital	x		
	Other hospital			
Pre-hospital diagnosis	Yes	x		
	No			
Pre-hospital anesthesia	Yes	x		
	No			
STESS	2		x	
	3			
	4			
	5			
Refractoriness	Non-RSE		x	
	RSE			
	SRSE			
OUTCOME				
Condition at discharge	Worse			x
	Baseline			
GOS at discharge	≤3			x
	>3			
Mortality at discharge	Yes			x
	No			

3.5.3 Outcome parameters

Mortality was calculated over the treatment period in HUCH. No post-discharge follow-up was performed in this study. Cessation of GCSE was determined with three parameters used as markers for cessation: BS, seizure freedom and return of consciousness. Outcome of the patients was defined based on functional outcome and mortality at hospital discharge. Functional outcome was assessed using Glasgow Outcome Scale (GOS 1-3 for bad outcome, GOS >3 for good outcome) and condition relative to baseline condition (worse-than-baseline vs. baseline) at hospital discharge. Functional outcome was considered good if the patient returned to his/her baseline condition and GOS at hospital discharge was >3. Outcome measures at hospital discharge were collected from the medical records.

While processing the pre-hospital part of this study (II), some coding rules were sharpened regarding pre-hospital procedures of the treatment. They were more clearly defined to the above-mentioned form. This induced some incoherence in results between studies I and II, affecting delay parameters Onset-to-alarm, Alarm-to-EMS, Onset-to-first-ED, EMS-arrival-to-first-ED, Onset-to-initial-treatment and grouping variables SE onset, Effect of the initial treatment and pre-hospital diagnosis. Changes to the results (study I) proved to be minimal and insignificant and the amended results according to renewed coding rules are presented in the results section in Table 8. and 9.

3.6 Statistical analysis

The results are expressed as median (min-max)/mean (SD) and/or range/interquartile range (IQR) or as number of patients and percentage. Statistical significance was defined as $p < 0.05$ and two-tailed tests were used. Statistical analyses were executed using the SPSS software (versions 20.0 (I), 21.0 (II), 22.0 (III), 24.0 (IV), SPSS, IBM Corp. USA).

Study I

Statistical significance of the differences in variables between independent samples was tested with the non-parametric Wilcoxon-Mann-Whitney test. Differences in categorical variables were examined using Chi-square test.

Study II

The Mann–Whitney and the Kruskal–Wallis tests were used to find out differences in the univariate analysis between the patient groups. The Dunn's test was used in post hoc comparisons. Multivariate analysis was performed with generalized linear modelling. Bootstrap resampling (1000 samples) was used to calculate the bias corrected percentile confidence intervals. Clinically relevant, plausibly important grouping variables were included in the model: SE type 1, SE type 2, Epilepsy, Scene at SE onset, Initial treatment before EMS and First ED. First ED was removed from the models, if it was chronologically irrelevant.

Study III

The normality of variables was tested with the Kolmogorov-Smirnov test. For the non-normal data, the Spearman's correlation coefficient and, for normally distributed data, the Pearson's correlation coefficient were calculated to find out correlation between continuous variables. Bootstrap resampling (1000 samples) was used to calculate the bias corrected percentile confidence intervals for correlation coefficients. Statistical significance of the differences in variables between independent samples was tested with the nonparametric Wilcoxon-Mann–Whitney test. Differences in categorical variables were examined using the Fisher's exact test. The Kaplan-Meier analysis with the log-rank test was used to

analyze time-to-event data. Linear regression analysis with bootstrap resampling (5000 samples) was used to model delays in treatment response.

Study IV

The Mann-Whitney test was used to find out differences in continuous variables. Logistic regression analysis was used to find out risk factors/delays for each outcome. Log transformation was used for time variables in logistic regression analysis. Bootstrap resampling (1000 samples) was used to calculate bias corrected percentile confidence intervals for odds ratios. Receiver operating characteristics (ROC) curves were created, and optimal cut-off values were calculated by maximizing the Younden's index.

4 RESULTS

4.1 Validity of data

Reporting bias of time points in this retrospective study was controlled with careful evaluation of the coverage and accuracy of data obtained from the medical documents. Table 7. shows average L_{WAS} and DA values in studies I-IV. The overall precision of recording practices and delay data coverage is considered acceptable, based on the evaluation of the data availability (mean DA = 93.7 – 98.3%) and accuracy (mean L_{WAS} = 1.4 - 1.6). The latter indicates data accuracy with less than 5 min deviation from the absolute accuracy. L_{WAS} and DA values improved during the SE period, in pre-hospital phase L_{WAS} ranged from 1.4 to 2.3, whereas in-hospital recordings it approached L_{WAS}=1.

Table 7. Average accuracy (L_{WAS}) and availability (DA) of the data in studies I-IV.

	L_{WAS}	DA
Study I	1,4	93,7
Study II	1,6	95,4
Study III	1,6	97,4
Study IV	1,5	98,3

Missing data consisted mainly of category “events missing”. Because of the heterogeneity of the course of SE/GCSE, not every patient needed anesthesia, obtained BS or was treated in ICU. Onset-to-alarm, onset-to-initial-treatment and onset-to-first-ED times were missing in some patients due to timing of the events during the pre-status period. Unknown data concerned only single parameters for a few patients.

4.2 Patient characteristics

Basic patient characteristics, SE etiologies and predisposing factors, as well as parameters regarding SE type-, patient- and SE episode- related factors and outcome are presented in Table 8. and 9.

Table 8. Characteristics of SE (I-II) and GCSE (III-IV) patients. Values marked with (*) are corrected values and different compared to original articles. (Part 1/2)

VARIABLE		SE (I-II)		GCSE (III-IV)	
		N	%	N	%
All		82	100	70	100
PATIENT CHARACTERISTICS					
AGE	Mean	55		54,3	
	Range	16-85		16-85	
GENDER	Male	42	51	35	50,0
	Female	40	49	35	50,0
MEDICAL HISTORY	Previous recorded illnesses	81	98,8	70	100
	Epilepsy	51	62,2	46	65,7
ETIOLOGIES	Epilepsy	52	63,4	46	65,7
	Acute brain disorder	11	13,4	7	10,0
	Prior brain disorder	8	9,8	7	10,0
	Unknown	12	14,6	10	14,3
PREDISPOSING FACTORS	Inappropriate epilepsy medic	19	23,2	16	22,9
	Alcohol	12	14,6	11	15,7
	Physical / emotional stress	10	12,2	10	14,3
	Hyponatremia	6	7,3	5	7,1
	Systemic febrile infection	5	6,1	5	7,1
	Sleep deprivation	2	2,4	2	2,9
	Other	9	11	6	8,6
SE TYPE RELATED FACTORS					
SE type 1	CSE	74	90,2	70	100
	NCSE	8	9,8	0	0
SE type 2	GSE	76	92,7	70	100
	Focal	6	7,3	0	0
Pre-status period	Yes	15	18,3	14	20
	No	67	81,7	56	80
SE onset	Continuous	54*	64,6	45	64,3
	Intermittent	28*	34,1	25	35,7
PATIENT RELATED FACTORS					
Epilepsy	Yes	51	62,2	46	65,7
	No	30	36,6	23	32,9
Age under 65	Yes	60	73,1	51	72,9
	No	22	26,8	19	27,1
Living	Home	28	34,1	20	28,6
	Home with someone else	35	42,7	32	45,7
	Nursing home	17	20,7	16	22,9

Table 9. Characteristics of SE (I-II) and GCSE (III-IV) patients. Values marked with (*) are corrected values and different compared to original articles. (Part 2/2)

VARIABLE		SE (I-II)		GCSE (III-IV)	
		N	%	N	%
All		82	100	70	100
SE EPISODE RELATED FACTORS					
Scene at SE onset	Home	37	45,1	31	44,3
	Healthcare unit	32	39	28	40
	Public place	13	15,9	11	15,7
SE onset at home, pt living a	Yes	13	15,9	9	12,9
	No	23	28	21	30
Initial treatment before EMS	Yes	20	24,4*	18	25,7
	No	54*	65,9	46	65,7
Rectiol as initial treatment	Yes	23	31,7	23	37,1
	No	54	67,1	44	62,9
Effect of the initial treatmen	Yes	17*	20,7	17	24,3
	No	45*	59,8	39	55,7
	Spontaneous cessation	15*	19,5	11	15,7
First ED	Tertiary hospital	58	70,7	51	72,9
	Other hospital	24	29,3	19	27,1
Pre-hospital diagnosis	Yes	27*	29,3	26	37,1
	No	53*	69,3	43	61,4
Pre-hospital anesthesia	Yes	26	31,7	24	34,3
	No	45	54,9	38	54,3
Anesthetic treatment	No Anesthesia	11	13,4	8	11,4
	Only Propofol	61	74,4	56	80
	Multiple Anesthetics	10	12,2	6	8,6
STESS	0	3	3,7	0	0
	1	2	2,4	0	0
	2	35	42,7	35	50
	3	19	23,2	16	22,9
	4	12	14,6	10	14,3
	5	9	11	9	12,9
	6	2	2,4	0	0
Refractoriness	Non-RSE	11	13,4	8	11,4
	RSE	31	37,8	30	42,9
	SRSE	40	48,8	32	45,7
OUTCOME PARAMETERS					
Condition at discharge	Worse	48	58,5	41	58,6
	Baseline	33	40,2	29	41,4
GOS at discharge	≤3	34	41,5	28	40
	>3	47	57,3	42	60
Mortality at discharge	Yes	7	8,5	5	7,1
	No	75	91,5	65	92,9

In studies I and II 70 cases (85.4%) presented with GCSE, 4 cases (4.9%) with focal convulsive SE and 8 cases (9.8%) with non-convulsive SE (6 generalized and 2 focal). 71 cases (86,6%) had SE refractory to first- and second-stage treatment. 18.3% of the cases presented with sporadic seizures preceding SE onset.

In 37 cases (45.1%) SE onset occurred at home, in 32 cases (39%) in a healthcare unit and in 13 cases (15.9%) in a public place. SE onset occurred outside the hospital in 74 cases (90.2%). EMS unit was called after the onset of SE in 67 (81.7%) cases. Among the rest of the cases, alarm call was made during the pre-SE period or the patient was already in hospital or arriving at the first ED otherwise. In 18 cases (21.9%) a physician-staffed rescue unit was recruited in addition to a normal EMS unit for quick intubation or induction of third-stage treatment. In 24 cases (29.3%) the first ED was hospital ED other than HUCH and these cases were later transported to tertiary hospital ED in HUCH. 10 out of these cases (41.7%) found their way independently to first ED or were transported by ambulance to the first ED during pre-SE period. 14 cases (58.3%) had ongoing SE, when they were transferred to other hospital ED, these cases included SE presenting with intermittent convulsions or unconsciousness.

For 78 SE cases (96.3%) the initial medication was first-stage medication and every third patient received it in rectal formulation. 61 out of the pre-hospital onset SE cases (82.4%) were medicated out-of-hospital. 20 cases of all cases (24.4%) received initial medication before EMS arrival, mainly in healthcare units. GCSE cases received average initial doses of 8.2 mg diazepam or 2.1 mg lorazepam. 62 cases (88.6%) were medicated with additional doses of up to 29.5 mg of diazepam or 6.5 mg lorazepam before intensifying the treatment to second- or third-stage medications. 77 SE cases (93.9%) were treated with second-stage medication. 35 cases (45.5 %) received second-stage medication before anesthesia, whereas 32 cases (41.6 %) received it after induction of the anesthesia. 71 SE cases (86.8%) were anesthetized, all receiving propofol. 8 cases (11.2%) needed change of anesthetic agent. 53 cases (64.6 %) had only one anesthesia period, while 18 cases (22.0 %) needed more than one period because of withdrawal seizures and ongoing SE. Anesthetic treatment was inducted out-of-hospital in 26 cases (31.7%).

SE diagnosis was made on clinical grounds in 74 cases (90.2%) and based on EEG in 8 cases (9.8%). The diagnosis was reached pre-hospitally in 27 (29.3%) cases, in 10 cases by paramedics. EEG was recorded in 67 cases (81.7 %): eight (11.9 %) for diagnosis and the rest for verification of treatment response. Continuous EEG-monitoring was available for 50 cases (70.4% in the anesthetized cases).

Mortality was 8.5% among all types of SE patients. Five out of the seven deceased patients died of direct effects of SE. Two died of complications, pneumonia and PRIS. At hospital discharge five patients (6.1%) remained unconscious. In 40.2% of SE cases the patient´s condition returned to baseline and in 57.3% of the cases the condition was considered good (GOS>3). 29 cases (35.4 %) were discharged to home, 45 cases (54.9 %) needed rehabilitation in another hospital or nursing home and for one case the data was not available.

4.3 Delays (I)

The clinical course of SE was systematically analyzed and main delay components were defined as delays in the treatment and treatment response delays. Delays in the treatment were subdivided into pre-hospital, diagnostic and treatment delays. Also, specific periods in the treatment course of SE were defined. The lengths of the individual delay components are presented in Table 10. Also, the delays of the GCSE patients, handled in studies III and IV, are presented here.

Median 47 minutes of the 2h 2min pre-hospital period elapsed before the EMS arrived at the scene. Median 75 minutes were spent on treatment procedures on site and transportation to the ED. The time of EMS arrival after the alarm covered only 7% (median 9 min) of the total pre-hospital delay. A considerable extra delay was generated in cases needing a physician-staffed unit.

Table 10. Median delays in the management of SE (I-II) and GCSE (III-IV). Values marked with (*) are corrected values and different compared to original articles.

VARIABLE	SE (I-II)				GCSE (III-IV)			
	N	%	TIME		N	%	TIME	
ALL	82	100	Median	Range	70	100	Median	Range
DELAYS IN THE TREATMENT								
PRE-HOSPITAL DELAYS								
Onset-to-alarm (Standard Ambulance)	67*	81,7*	0:38	00:00 - 57:44	60	85,7	0:36	00:00 - 57:44
Physician staffed rescue unit	18*	21,9*	1:15	00:03 - 05:00				
Alarm-to-EMS (Standard Ambulance)	67*	81,7*	0:09	00:00 - 00:45				
Physician staffed rescue unit	18*	21,9*	0:20	00:05 - 00:48				
Onset-to-first-ED	70*	85,4*	2:02	00:00 - 58:29	62	88,6	2:02	00:00 - 58:29
EMS-arrival-to-first-ED	67*	81,7*	0:59	00:10 - 03:02				
Onset-to-tertiary-hospital (HUCH)	82	100,0	2:25	00:37 - 277:40	70	100	2:25	00:37 - 277:40
DIAGNOSTIC DELAYS								
Onset-to-diagnosis	82	100,0	2:10	00:06 - 70:40	70	100	1:48	00:06 - 60:06
Clinical diagnosis	74	90,2	1:50	00:06 - 60:06				
Diagnosis based on EEG	8	9,8	13:20	2:55 - 70:40				
Onset-to-EEG	67	81,7	22:02	2:30 - 142:00	57	81,4	21:52	2:30 - 142
Diagnostic EEG	8	9,8	15:30	5:20 - 70:40				
Treatment response EEG	59	72,0	22:32	2:30 - 142:00				
Onset-to-EEG-monitoring	50	61,0	12:00	2:30 - 82:14	42	60,0	11:10	2:30 - 82:14
HUCH-ED-to-cEEG	50	61,0	7:30	1:30 - 27:40				
Anesthesia-to-cEEG	50	61,0	5:59	00:30 - 29:55				
HUCH-ED-to-etiological-investigation								
CT of the head	73	89,0	2:34	00:26 - 64:00				
MRI of the head	17	20,7	145:40	2:15 - 617:50				
Lumbar puncture	30	36,6	26:55	3:55 - 134:05				
Sign. laboratory finding	27	32,9	2:32	00:06 -12:15				
TREATMENT DELAYS								
Onset-to-initial-treatment	77*	93,9*	0:35	00:00 - 77:05	67	95,7	0:30	00:00 - 8:15
Onset-to-second-stage-medication	77	93,9	3:00	00:30 - 77:05	67	95,7	2:40	00:30 - 61:54
Onset-to-anesthesia	71	86,6	2:55	00:00 - 81:45	62	88,6	2:38	00:00 - 66:20
TREATMENT RESPONSE DELAYS								
Onset-to-first-convulsion-end	82	100,0	0:55	00:01 - 63:40	70	100	0:51	00:01 - 63:40
Onset-to-Burst-suppression	38	53,5	17:30	5:05 - 137:50	30	42,9	14:42	5:05 - 137:50
Anesthesia -to-BS	38	53,5	10:31	00:00 - 132:15				
Duration of first BS	38	53,5	13:00	00:30 - 40:40				
Onset-to-seizure-freedom	74	90,2	5:52	00:26 - 533:15	70	100	5:15	00:26 - 533:15
RSE/SRSE cases	65	79,2	6:45	00:26 - 533:15				
Non-RSE cases	9	10,9	1:52	00:32 - 59:19				
Total-convulsion-time (convulsive cases)	74	90,2	1:36	00:04 - 63:51				
Onset-to-consciousness	71	86,6	47:40	2:40 - 744:15	61	87,1	42:45	2:40 - 444:40
Non-RSE cases	8	9,8	7:05	1:20 - 83:22				
PERIODS IN THE TREATMENT								
Pre-status-period	15	18,3	2:10	00:30 – 41:00				
Total-anesthesia-time	71	86,6	38:00	3:35 - 238:52	62	88,5	38:00	3:35 - 238:52
Total-ICU-time	73	89,0	64:15	7:45 - 529:30	63	90	58:40	7:45 - 520:25
HUCH-treatment-period	82	100,0	7,7 days	0,41 - 64,7 days				

The diagnostic delay was significantly longer in cases diagnosed by EEG than in cases diagnosed on clinical grounds ($p<0.0001$). The delay in recording the EEG did

differ between EEGs performed for diagnostic purposes and those intended for treatment response evaluation.

4.4 Pre-hospital factors (II)

The multivariate analysis of the factors associated with delays in the pre-hospital management of SE is presented in Figure 3(a-f). Focal SE was significantly associated with long onset-to-initial-treatment (25.8h, 95%CI 0.4-60.3, p=0.049), onset-to-diagnosis (28.5h, 95%CI 6.2-53.3, p=0.002), and onset-to-anesthesia (36h, 95%CI 1.5-69.0, p=0.002) times. Administration of the initial treatment before EMS arrival was significantly associated with long onset-to-alarm (4h, 95%CI 0.7-7.3, p=0.024) and onset-to-first-ED (4.3h, 95%CI 1.2-8.8, p=0.036) times. Primary admission to a hospital other than tertiary hospital ED caused a significant delay in onset-to-diagnosis (8.8h, 95%CI 1.8-15.4, p=0.008) and onset-to-anesthesia (9.8h, 95% CI 2.6-17.8, p=0.019) times.

Post Hoc analysis revealed that, if SE onset occurred in a healthcare unit, the delays onset-to-alarm (p< 0.001), onset-to-first-ED (p<0.001), onset-to-tertiary-hospital (p<0.001), onset-to-diagnosis (p=0.017), and onset-to-anesthesia (p=0.006) were significantly longer than if SE occurred in a public place. Living at home with someone else was associated with shorter onset-to-tertiary-hospital time than living in a nursing home (p=0.023). Onset-to-initial-treatment time was not associated with effectiveness of the medication. On the contrary, spontaneous cessation of the first seizure was associated with long onset-to-initial-treatment time.

In the univariate analysis pre-status period (p=0.031) and rectiol as initial treatment (p=0.011) were associated with short onset-to-initial-treatment time. Age under 65 was associated with short onset-to-first-ED time (p=0.040) and both pre-hospital diagnosis and pre-hospital anesthesia were associated with short onset-to-diagnosis and onset-to-anesthesia times (all p<0.001). Patients, who lived with someone and whose SE occurred at home, had shorter onset-to-initial-treatment (p=0.004), onset-to-tertiary-hospital (p=0.042), onset-to-diagnosis (p=0.002) and onset-to-anesthesia (p=0.015) delays, than patients living alone.

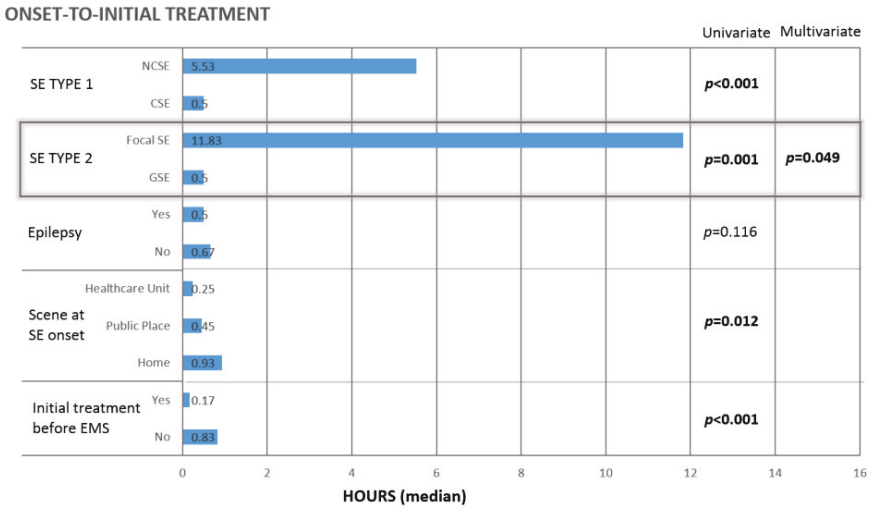

ONSET-TO-INITIAL TREATMENT
Univariate
Multivariate
SE TYPE 1
NCSE
5.53
CSE
0.5
p<0.001
SE TYPE 2
Focal SE
11.83
GSE
0.5
p=0.001
p=0.049
Epilepsy
Yes
0.5
No
0.67
p=0.116
Scene at SE onset
Healthcare Unit
0.25
Public Place
0.45
Home
0.93
p=0.012
Initial treatment before EMS
Yes
0.17
No
0.83
p<0.001
0
2
4
6
8
10
12
14
16
HOURS (median)

Fig 3a.

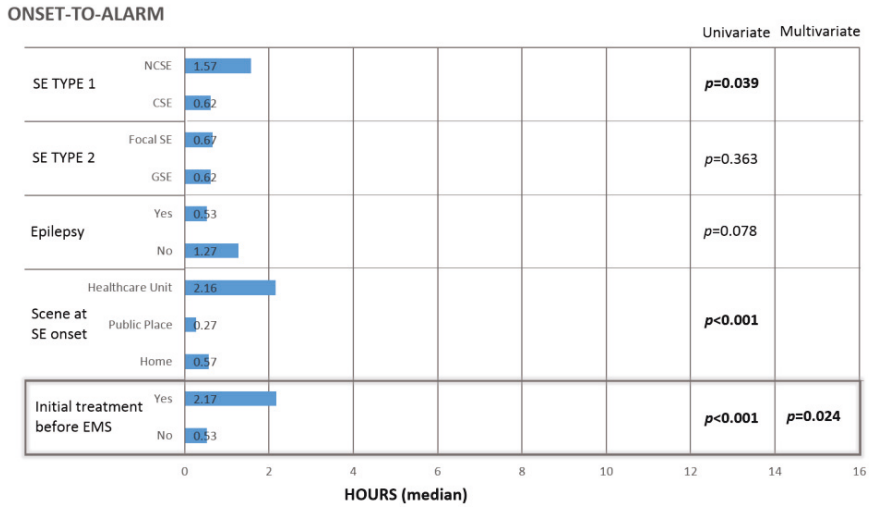

ONSET-TO-ALARM
Univariate
Multivariate
SE TYPE 1
NCSE
1.57
CSE
0.62
p=0.039
SE TYPE 2
Focal SE
0.67
GSE
0.62
p=0.363
Epilepsy
Yes
0.53
No
1.27
p=0.078
Scene at SE onset
Healthcare Unit
2.16
Public Place
0.27
Home
0.57
p<0.001
Initial treatment before EMS
Yes
2.17
No
0.53
p<0.001
p=0.024
0
2
4
6
8
10
12
14
16
HOURS (median)

Fig 3b.

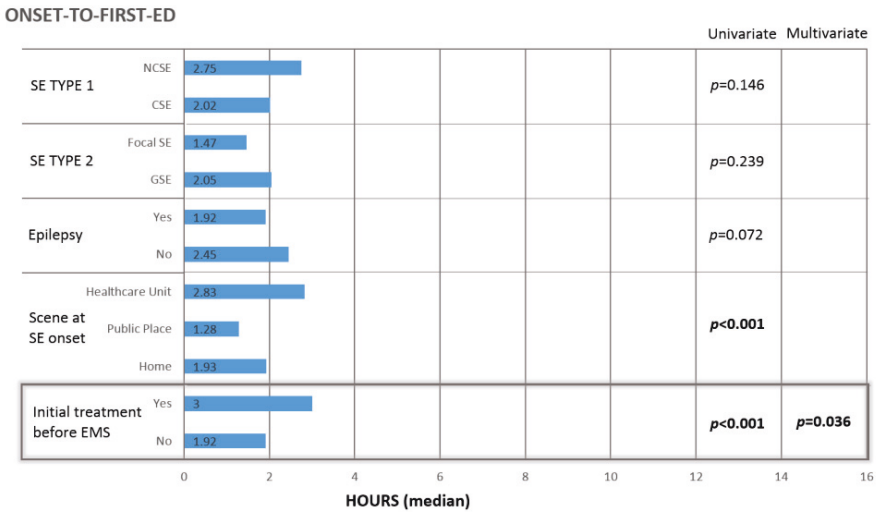

ONSET-TO-FIRST-ED
Univariate
Multivariate
SE TYPE 1
NCSE
2.75
CSE
2.02
p=0.146
SE TYPE 2
Focal SE
1.47
GSE
2.05
p=0.239
Epilepsy
Yes
1.92
No
2.45
p=0.072
Scene at SE onset
Healthcare Unit
2.83
Public Place
1.28
Home
1.93
p<0.001
Initial treatment before EMS
Yes
3
No
1.92
p<0.001
p=0.036
0
2
4
6
8
10
12
14
16
HOURS (median)

Fig 3c.

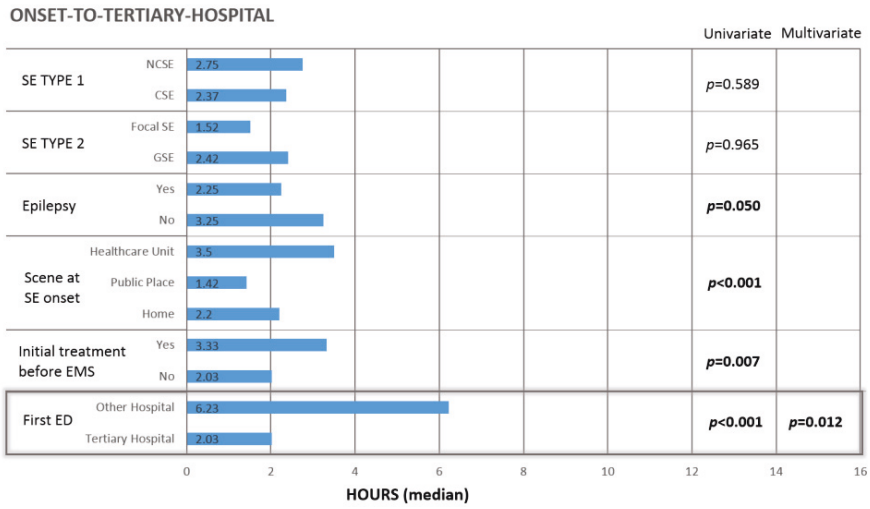

ONSET-TO-TERTIARY-HOSPITAL
Univariate
Multivariate
SE TYPE 1
NCSE
2.75
CSE
2.37
p=0.589
SE TYPE 2
Focal SE
1.52
GSE
2.42
p=0.965
Epilepsy
Yes
2.25
No
3.25
p=0.050
Scene at SE onset
Healthcare Unit
3.5
Public Place
1.42
Home
2.2
p<0.001
Initial treatment before EMS
Yes
3.33
No
2.03
p=0.007
First ED
Other Hospital
6.23
Tertiary Hospital
2.03
p<0.001
p=0.012
0
2
4
6
8
10
12
14
16
HOURS (median)

Fig 3d.

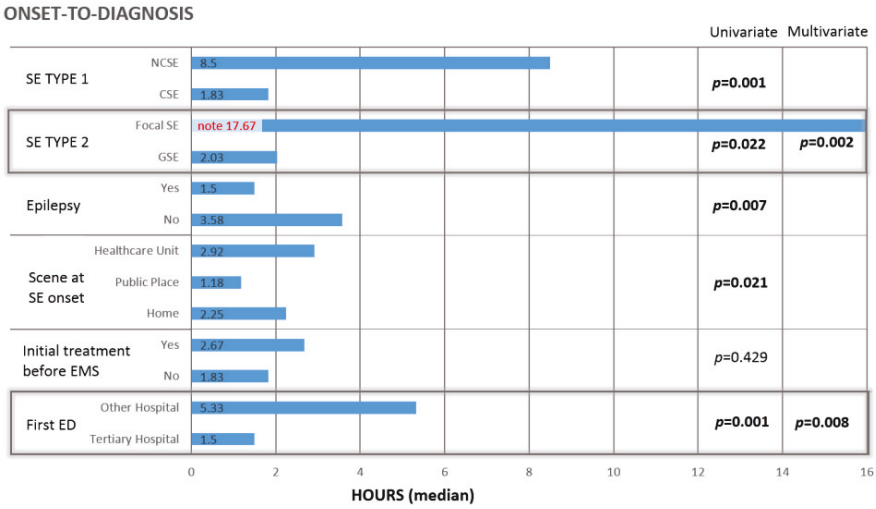


Fig 3e.

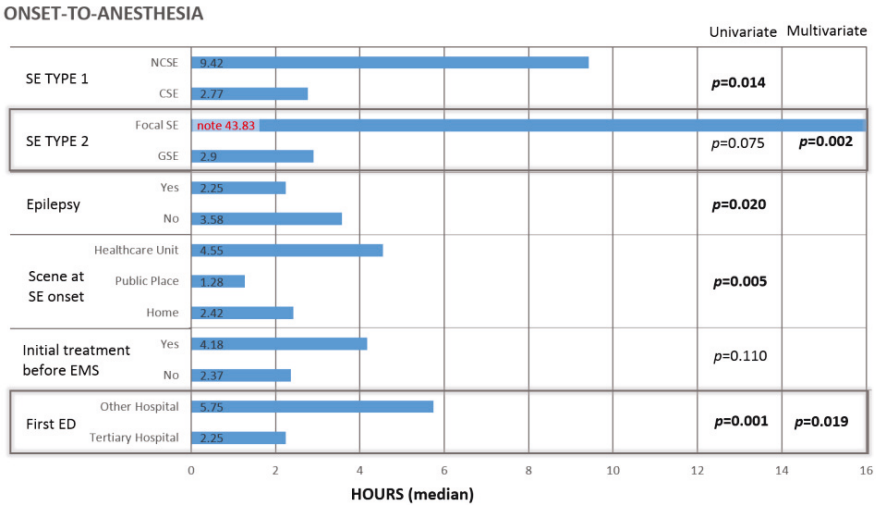


Fig 3f.

Fig. 3(a-f). Univariate analysis of the factors related to pre-hospital delays in management of SE. Median delays of the patient groups selected to multivariate analysis and results of the multivariate analysis are also presented

Kaplan-Meier curve Fig. 4. shows the difference in onset-to-diagnosis time, when patients transported directly to the tertiary hospital ED were compared with those treated first in another hospital ED. These groups differed from each other also in terms of onset-to-second-stage-medication time ($p < 0.045$), and onset-to-anesthesia time ($p < 0.001$).

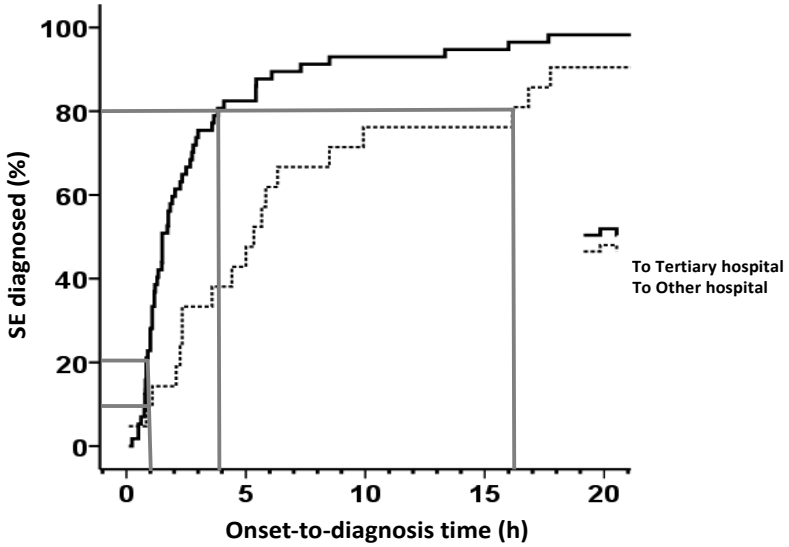


Fig 4. Kaplan-Meier curve showing the difference of the Onset-to-diagnosis time between the SE patient groups triaged primarily to tertiary hospital ED or to other hospital ED.

4.5 Cessation of GCSE (III)

Chronological correlations, correlations between onset-to-event and event-to-treatment-response-delays (markers for cessation of SE), are shown in Table 11. The delays in giving the second-stage medication ($p=0.027$), obtaining BS ($p=0.005$) and achieving clinical seizure freedom ($p =0.035$) correlate significantly with the delay in return of consciousness. Statistically significant negative correlation between full-scale EEG delay and BS delay is clinically insignificant, since in 76.7% of the BSs were registered with cEEG before full scale EEG.

Table 11. Chronological correlations between the onset-to-event delays and event-to-treatment-response delays of GCSE patients.

VARIABLE	EVENT-TO-BURST-SUPPRESSION				
ONSET-TO-EVENT	**N**	**Coefficient**	**95% CI (min)**	**95% CI (max)**	**P-VALUE**
Onset-to-initial-treatment	28	0.005	-0.421	0.412	0.981
Onset-to-first-convulsion-end	29	0.109	-0.282	0.474	0.573
Onset-to-alarm	22	0.303	-0.176	0.666	0.171
Onset-to-diagnosis	29	0.169	-0.198	0.497	0.382
Onset-to-second-stage-medication	30	0.057	-0.345	0.421	0.765
Onset-to-anesthesia	30	- 0.152	-0.488	0.175	0.424
Onset-to-first-ED	23	0.343	-0.062	0.732	0.109
Onset-to-tertiary-hospital (HUCH)	30	0.113	-0.247	0.498	0.552
Onset-to-EEG	26	-0.753	-0.914	-0.473	**<0.001**
Onset-to-EEG-monitoring	30	-0.183	-0.579	0.278	0.332
Onset-to-Burst-suppression					
Onset-to-clinical-seizure-freedom					

VARIABLE	EVENT-TO-CLINICAL-SEIZURE FREEDOM				
ONSET-TO-EVENT	**N**	**Coefficient**	**95% CI (min)**	**95% CI (max)**	**P-VALUE**
Onset-to-initial-treatment	65	-0.095	-0.344	0.156	0.453
Onset-to-first-convulsion-end	68	-0.112	-0.360	0.136	0.362
Onset-to-alarm	55	0.020	-0.253	0.295	0.883
Onset-to-diagnosis	68	-0.069	-0.321	0.226	0.574
Onset-to-second-stage-medication	66	-0.046	-0.323	0.265	0.713
Onset-to-anesthesia	61	-0.057	-0.333	0.211	0.662
Onset-to-first-ED	60	-0.022	-0.296	0.271	0.870
Onset-to-tertiary-hospital (HUCH)	69	-0.037	-0.285	0.195	0.761
Onset-to-EEG	54	-0.198	-0.475	0.081	0.152
Onset-to-EEG-monitoring	41	-0.051	-0.386	0.279	0.752
Onset-to-Burst-suppression	30	0.031	-0.359	0.443	0.872
Onset-to-clinical-seizure-freedom					

VARIABLE	EVENT-TO-CONSCIOUSNESS				
ONSET-TO-EVENT	**N**	**Coefficient**	**95% CI (min)**	**95% CI (max)**	**P-VALUE**
Onset-to-initial-treatment	56	-0.012	-0.237	0.205	0.928
Onset-to-first-convulsion-end	58	0.085	-0.173	0.322	0.528
Onset-to-alarm	47	-0.087	-0-364	0.223	0.563
Onset-to-diagnosis	59	0.037	-0.267	0.322	0.783
Onset-to-second-stage-medication	56	0.295	0.039	0.534	**0.027**
Onset-to-anesthesia	51	0.025	-0.251	0.330	0.859
Onset-to-first-ED	52	0.101	-0.195	0.385	0.477
Onset-to-tertiary-hospital (HUCH)	59	0.068	-0.220	0.338	0.610
Onset-to-EEG	46	-0.162	-0.420	0.116	0.283
Onset-to-EEG-monitoring	31	0.101	-0.311	0.459	0.588
Onset-to-Burst-suppression	21	0.584	0.058	0.863	**0.005***
Onset-to-clinical-seizure-freedom	59	0.275	-0.036	0.563	**0.035**

Spearman's rho

* Pearson's rho

Regression analysis of the effect of the chronological delay components on clinical seizure freedom and return of consciousness is presented in Table 12. Prolonged delay between initial treatment and second-stage treatment is associated with longer delays in attaining clinical seizure freedom and return of consciousness (p=0.021, p=0.002, respectively). Also, the time between initial treatment and SE diagnosis is associated with delayed clinical seizure freedom (p=0.016).

Table 12. The regression analysis of the effect of the chronological delay components on markers for cessation of GCSE.

VARIABLE	TIME (h)	95% CI min	95% CI max	p
ONSET-TO-CLINICAL-SEIZURE-FREEDOM				
Intercept	9,0	-1,4	23,6	0.082
Onset-to-initial-treatment	7,8	-1,6	13,2	0,008
Initial-treatment-to-diagnosis	2,3	0,2	4,2	**0,016**
Intercept	8,2	-5,6	31,3	0,273
Onset-to-initial-treatment	6,6	-2,8	11,6	0,035
Initial-treatment-to-second-stage-medication	3,0	0,4	4,8	**0,021**
ONSET-TO-CONSCIOUSNESS				
Intercept	38,1	14,8	73,4	0,008
Onset-to-initial-treatment	0,4	-15,2	8,1	0,935
Initial-treatment-to-second-stage-medication	9,7	3,9	15,8	**0,002**

Univariate analysis of the factors related to delays in cessation of GCSE and to the likelihood of return of consciousness showed, that SRSE cases have significantly longer delays in achieving clinical seizure freedom and returning consciousness than non-SRSE cases ($p < 0.001$). All the other factors remained insignificant.

Patients regaining consciousness (N=60, median 3.67 h, 95% CI 1.64–5.69 h, DA=98%, L_{WAS}=1.58) achieved clinical seizure freedom significantly earlier than patients remaining unconscious (N=9, median 41.17 h, 95% CI 14.87–67.46 h, DA=100%, L_{WAS}=1.67) (p=0.022). Differences in BS delays between these groups did not reach statistical significance.

4.6 Outcome (IV)

Univariate logistic regression analysis of the delays as risk factors for GCSE patients' outcome at hospital discharge is presented in Table 13. The long delay in reaching the tertiary hospital (p=0.034) was a significant risk factor for functional deterioration in relation to baseline condition. Long delays in onset-to-diagnosis (p=0.032), onset-to-second-stage-medication (p=0.023), onset-to-consciousness (p=0.027) times and long anesthetic treatment (p=0.043) were risk factors for low GOS score (1-3). Short delay in giving the initial AED (p=0.047), long delays in starting the anesthesia (p=0.003) and long delay in returning consciousness (p=0.008) were risk factors for in-hospital mortality.

Cut-offs for the significant delays in the univariate analysis predicting poor/worse-than-baseline condition were determined by plotting ROC-curves (Table 14. and Fig 5. Diagnostic delay over 2.4 hours (ODDS 3.9, 95%CI 1.4-11.0, p=0.011), delay in giving the second-stage-medication over 2.5 hours (ODDS 8.3, 95%CI 2.4-28.5, p=0.001), altered mental status or unconsciousness lasting over 41.5 hours (ODDS 5.0, 95%CI 1.5-16.9, p=0.009) and anesthetic treatment over 45.5 hours (ODDS 5.3, 95%CI 1.8-16.2, p=0.003) increased the risk of poor functional recovery (GOS 1-3). Delay over 2.1 hours before reaching the tertiary hospital increased the risk of worse-than-baseline condition at discharge (ODDS 3.2, 95%CI 1.2-8.8, p=0.023).

In the multivariate regression analysis, none of the delays were independent risk factors for poor functional outcome or mortality at hospital discharge.

Table 13. Univariate logistic regression analysis of the delays as risk factors for poor outcome at hospital discharge and summary of delay parameters. (p-values <0,05 are bolded, p values <0,01 are marked with *)

DELAYS	Median time	IQR	Time (h)	IQR	Time (h)	IQR	p	95%CI ODDs	Min	Max	p
CONDITION AT DISCHARGE	**All Cases**		**Worse**		**Baseline**						
Onset-to-initial-treatment	0,5	0,78	0,5	0,86	0,6	0,67	0,598	0,9	0,4	1,7	0,721
Onset-to-diagnosis	1,8	2,77	2,0	4,08	1,5	1,48	0,146	2,1	0,6	11,3	0,223
Onset-to-second-stage-treatment	2,7	3,39	3,2	3,89	2,3	1,98	0,087*	2,6	0,5	41,8	0,247
Onset-to-tertiary-hospital	2,4	2,83	2,6	3,47	2,0	2,35	**0,027**	4,4	1,4	47	**0,034**
Onset-to anesthesia	2,6	4,04	2,3	4,48	3,2	2,33	0,256	2	0,67	7,7	0,233
Onset-to-Burst-Suppressio	14,7	19	14,9	21,79	14,0	19,27	0,632	2,3	0,1	226,8	0,461
Onset-to-seizure-freedom	5,3	46,6	5,8	49,36	4,1	35,4	0,599	1,2	0,7	2,5	0,515
Onset-to-consciousness	42,8	51	56,3	65,33	29,0	43,83	0,082*	2,5	0,8	15,2	0,095*
Total-anesthesia-time	38,0	51,23	46,8	65,57	24,0	29,81	0,059*	3,5	0,9	30,6	0,117
Total-ICU-time	58,7	106,75	67,6	111,4	50,3	90,25	0,106	2,9	0,8	12,2	0,08*
GOS AT DISCHARGE			**GOS 1-3**		**GOS>3**						
Onset-to-initial-treatment	0,5	0,78	0,5	1	0,5	0,75	0,966	1,1	0,6	2,2	0,846
Onset-to-diagnosis	1,8	2,77	2,7	4,33	1,5	1,59	0,071*	3,4	1	20,6	**0,032**
Onset-to-second-stage-treatment	2,7	3,39	3,4	4,58	2,3	2,08	**0,007**	6,6	1,3	101,5	**0,023**
Onset-to-tertiary-hospital	2,4	2,83	2,4	3,95	2,1	2,21	0,074*	2,4	0,8	19,7	0,162
Onset-to anesthesia	2,6	4,04	4,3	4,84	2,3	2,29	**0,048**	3,1	0,92	15,2	0,059*
Onset-to-Burst-Suppressio	14,7	19	16,5	32,96	13,3	17,84	0,587	2,3	0,1	44	0,444
Onset-to-seizure-freedom	5,3	46,6	7,5	55,76	4,3	31,31	0,229	1,6	0,8	3,6	0,178
Onset-to-consciousness	42,8	51	59,9	63,77	28,5	43,67	**0,032**	3,6	1,1	37,7	**0,027**
Total-anesthesia-time	38,0	51,23	57,9	57,87	26,5	39,5	**0,037**	5,1	0,9	52,5	**0,043**
Total-ICU-time	58,7	106,75	69,7	100,17	53,3	109,88	0,114	3	0,8	12,5	0,054*
IN-HOSPITAL MORTALITY			**Dead**		**Alive**						
Onset-to-initial-treatment	0,5	0,78	0,2	0,83	0,5	0,7	0,115	0,4	0	1,7	**0,047**
Onset-to-diagnosis	1,8	2,77	4,3	6,46	1,8	2,65	0,208	2,9	0,3	35,5	0,209
Onset-to-second-stage-treatment	2,7	3,39	3,6	4,93	2,6	2,78	0,467	1,4	0	28,2	0,741
Onset-to-tertiary-hospital	2,4	2,83	2,8	49,48	2,3	2,78	0,172	2,6	0,2	7,71E+75	0,123
Onset-to anesthesia	2,6	4,04	7,5	35,43	2,4	3,65	**0,031**	8,7	1,2	1,33E+03	**0,003**
Onset-to-Burst-Suppressio	14,7	19	22,0	18	14,0	19,08	0,22	5,1	0,6	2657,1	0,168
Onset-to-seizure-freedom	5,3	46,6	8,4	92,89	4,7	47,54	0,3	1,8	0,5	51,4	0,252
Onset-to-consciousness	42,8	51	89,3	0	40,4	50,43	0,475	6,3	3,1	30,6	**0,008**
Total-anesthesia-time	38,0	51,23	76,5	68,26	34,4	48,71	0,202	6,6	0,2	849,8	0,153
Total-ICU-time	58,7	106,75	65,9	115,15	58,6	111,42	0,613	1,8	0,3	15,5	0,463

For logistic regression the variables were log transformed and bootstrapped confidence intervals (CI) were calculated.

Table 14. Area under curve (AUC) and cut-offs for the significant delays.

VARIABLES DELAY	OUTCOME	AUC	CI 95% (min)	CI 95% (Max)	p	CUT-OFF (h)	Sensitivity	Specificity
Onset-to-diagnosis	GOS 1-3	0,63	0,49	0,77	0,071*	2,4*	0,76	0,56
Onset-to-second-stage-medication	GOS 1-3	0,693	0,56	0,83	**0,008**	**2,5**	0,59	0,85
Onset-to-tertiary-hospital (HUCH)	Worse-than-baseline condition	0,657	0,52	0,79	**0,028**	**2,1**	0,71	0,57
Onset-to-consciousness	GOS 1-3	0,658	0,52	0,80	**0,037**	**41,5**	0,75	0,64
Total-anesthesia-time	GOS 1-3	0,676	0,54	0,82	**0,032**	**45,4**	0,66	0,72

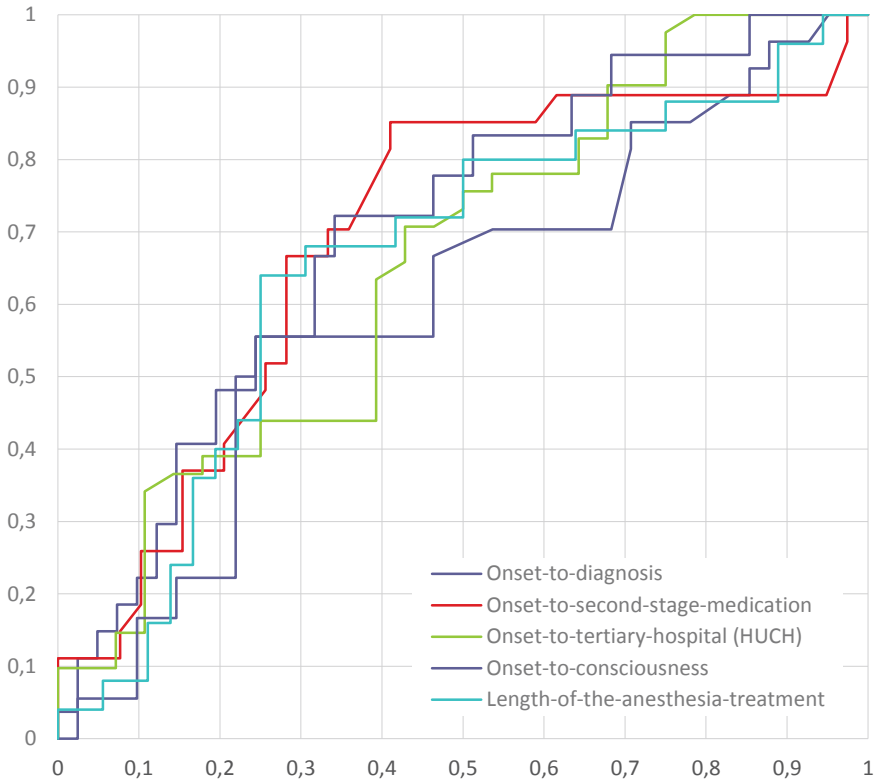


Fig 5. Receiver operating characteristics curves (ROC-Curves) for the delays. Outcome variable for onset-to-diagnosis, onset-to-second-stage-medication, onset-to-consciousness and total-anesthesia-time is low GOS score (1-3) at hospital discharge and for onset-to-tertiary-hospital (HUCH) is worse-than-baseline-condition.

5 DISCUSSION

This retrospective cohort study reveals unacceptably long delays in the treatment of SE, which calls for rigorous changes in the treatment management. Streamlining the whole treatment chain of SE is necessary and the main focus should be on pre-hospital management. Here delay-related factors and proposed measures to shorten different delays will be discussed in detail. Paucity of the studies concerning the effects of delays on outcome in the previous literature complicates comparison.

5.1 Treatment delays

5.1.1 Initial treatment

The delay in giving the initial medication in our SE cohort is one of the shortest among the previously reported delays[38,76,86,90,111,116,123,129,161,168], though not even close to the times recommended by the guidelines. Quickest treatment initiation was achieved when rectal administration of the medication was used, and therefore buccal midazolam, which became routine practice in EMS after the present patient material was collected, is expected to further shorten the treatment delay. Clinical appearance of SE and scene at onset seem to set the pace and accuracy for the treatment. Convulsion and generalization of the seizure and onset in a healthcare unit were significantly associated with a short delay in administration of the initial treatment. Also, first seizures during pre-status period were associated with early administration of the initial treatment, which may partly be due to low threshold in pre-status recruitment of EMS.

Surprisingly, our study showed that short delay in giving the initial medication is related to in-hospital mortality and does not expedite cessation of GCSE. This unexpected result could be explained by the finding that although non-survivors received the initial treatment several times quicker than survivors, all the other delays were multiple compared to the survivors. Additionally, an initial treatment given early, before EMS arrives, resulted in longer onset-to alarm and onset-to-first-ED times, as compared to the group, whose initial treatment was given after EMS arrival. The same phenomenon was seen in the healthcare unit-onset group with short onset-to-initial-treatment time but otherwise delayed actions. These

findings may reflect the risk involved in partial treatment response, i.e., false sense of security after the first given medication. We demonstrate that adequately started pre-hospital initial treatment does not necessarily mean short delays in other parts of the treatment chain, if the continuum of the treatment is hampered by a failing recognition of SE. Taken together, these observations point out that short initial treatment delay per se does not lead to a better outcome, unless the whole pre-hospital chain of recovery is optimized and therefore a (local) standardized pre-hospital management protocol upon established SE cases should be generated.

5.1.2 Second-stage treatment

The delay in giving second-stage treatment observed in our study, median 3 h, is somewhat longer than those in previous reports[111,116] and may partly be due to the fact, that second-stage treatment was not available in EMS by the time of material collection. In our recruitment area, if the first-stage medication given out-of-hospital failed, the general practice was intubation and initiation of third-stage treatment, as happened in over 40 % of our cases.

In this present study, onset-to-second-stage medication delay was correlated with delay in return of consciousness in GCSE patients. Prolonged time between initial treatment and second-stage treatment predicted delayed clinical seizure freedom and return of consciousness. Additionally, delayed second-stage treatment was associated with poor outcome at hospital discharge. Since this study material is nearly homogeneous in terms of the agent used, iv-phosphenytoin, it seems even more essential to minimize second-stage medication delay in order to improve the patients' outcome. 2.5 hours as the prognostic cut-off in giving second-stage medication should direct the focus of streamlining the treatment protocol in the pre-hospital phase.

We propose that administration of second-stage agents already by EMS out-of-hospital could reduce the delays, especially now that safety, tolerability and storage issues regarding phosphenytoin could be bypassed by using the newer agents. There is no real evidence that the use of newer agents would impair the prognosis[188-190] and therefore it is possible that any second-stage agent given in

adequate doses during the first 2.5 hours might improve the outcome. Naturally, an adequate evaluation of the patient by a physician should be obtained to ascertain the correct diagnosis before the medication and to maximize patient's safety during the medication.

5.1.3 Third-stage treatment

In our material 50 % of the cases were anesthetized within 3 h, which equals to previous reports[111]. Median duration of IVAD treatment was also consistent with the literature[34,102,112]. The anesthetic used was mainly propofol, which was well tolerated, and although one complication of PRIS (death) was seen, in 90 % of the cases propofol led to the intended response. Prognostic cut-off of total-anesthesia time (45.4h) was not exceeded, which may have had a positive impact on the tolerability.

Long delays in starting third-stage treatment were significantly associated with in-hospital mortality and had a trend-like association with poor outcome. Therefore, IVADs should be initiated as early as possible after the first-, and second-stage treatments fail. GCSE patients with previously diagnosed epilepsy seemed more likely to have short delays in starting anesthesia as compared to other SE types. Therefore, recognition and diagnostic procedures of seizures other than GCSE should be improved by e.g. applying EEG on site.

SE onset at a public place, SE diagnosed out-of-hospital and transportation of patients directly to tertiary hospital ED were associated with short delays in initiation of anesthesia. Therefore, procedures of the pre-hospital phase of the treatment should be in focus when streamlining the protocols.

Although IVAD treatment for almost two days predicts poor functional outcome at hospital discharge, it does not mean that the IVAD treatment should be limited to less than two days in all patients. Targeting IVADs quickly to right patients and preventing or minimizing complications during IVAD treatment seem to be essential in the prognosis of IVAD-treated patients.

5.2 Pre-hospital delays

Nearly half of the two-hour prehospital delay elapsed before the emergency service arrived at the scene and the rest was used for treatment at the scene by paramedics and for transportation to the hospital. Long delay in calling the ambulance exceeded previous reported delays only to a small extent[76,161] and may partly be explained by patient-related factors, such as alcohol abuse (15 % of cases) and patient living alone, as also reported in stroke studies[208]. However, we think that this delay predominantly reflects lack of fluency in pre-hospital management. SE onset in a healthcare unit and treatment initiation before calling the ambulance resulted in exceedingly long delays in calling the ambulance and reaching EDs, although treatment initiation was managed without delay. This may reflect an inborn source of delay: once the treatment is started, it automatically leads to delays caused by assessment of the treatment response and, if unresponsive, further treatment attempts in the same unit. Such delays naturally do not occur in a public place. These results accentuate the need to further improve education on appropriate timing of contact with EMS. In Finland patients diagnosed with epilepsy and their care-takers have received a standard instruction to call emergency service as soon as a seizure prolongs over 5 min or the patient does not recover normally after the seizure. The current results suggest further need for education among professionals, as well.

Long delay in reaching the tertiary hospital was associated with worse-than-baseline condition at discharge in this current study. The median onset-to-first-ED time of all patients and that of patients transported straight to the tertiary hospital did not diverge markedly. Thus, an effective treatment in hospital could have been started with similar delay for both groups. However, it took four times longer for 80 % of the patients to be diagnosed with SE, and significantly longer delays in starting second- and third-stage medications, if the patient was triaged to a hospital other than tertiary hospital. We conclude that treating SE patients in EDs, where the neurologist bears the main responsibility 24 hours a day, and where EEG is more often available, may lead to better quality of treatment and better prognosis. The prognostic cut-off of slightly over 2 hours in reaching tertiary hospital calls for prompt recognition of SE and direct transportation of even suspected SE cases to tertiary hospital. Only if physician-staffed units at scene could make the diagnosis and start efficient second- and third-stage medications,

the importance of the time between onset of SE and admission to tertiary hospital ED might be less important, as also stated in cardiac infarction studies[211]. More frequent recruitment of physician-staffed rescue units upon the primary alarm with highest priority and qualification of paramedics to intubate and stabilize the patient already at the scene would also help eliminate the significant extra delay caused by second alarm for a physician-staffed unit, as seen in this study.

5.3 Diagnostic delays

The median delay of SE diagnosis in this material was over 2 hours, whereas the diagnostic delay of GCSE patients remained under 2 hours, mainly due to the fact, that almost all of GCSE cases could be diagnosed on clinical grounds. Diagnostic delay was associated with low GOS score at hospital discharge and a prognostic cut-off for the delay lay at little over two hours. Although diagnostic delay did not affect the duration of SE, short time between initial treatment and SE diagnosis was associated with early seizure freedom. Therefore, shortening the diagnostic delay is crucial to improve the patients' outcome and to ensure rapid and adequate treatment of SE.

Previously diagnosed epilepsy, onset at a public place and primary transportation to tertiary centre were related to shorter diagnostic delays, whereas focal SE and NCSE, for which availability of EEG is essential for diagnosis, were associated with long delays. Easier recognition of convulsive SE is obvious. Severity of the patients' general condition may also lead to accelerated actions in the pre-hospital management, as seen in stroke studies[202,204,205]. Awareness of the risk of SE among epilepsy patients may facilitate SE diagnosis, but quicker diagnosis in tertiary hospital may reflect insufficient level of awareness of SE in primary and secondary health care units, which lack neurologists and EEG service and which do not treat SE patients on regular basis. Rapidity of diagnosis among public-onset cases may simply reflect the fact that majority of those patients were transported directly to tertiary hospital.

Improvement of EEG availability is indispensable for improving diagnostics of SE, since in our cohort diagnostic EEG could not be performed more urgently than EEG for response verification purposes. Routinely applied continuous EEG monitoring for hospitalized SE patients would serve both diagnostic and monitoring purposes.

Out-of-hospital eEEG using a rapidly applicable electrode cap and telemedical connection to the hospital might provide a method to facilitate the diagnosing process on site. Presently, this suggestion remains speculative, since studies on eEEG at emergency site are lacking. However, major attempts should be made to enable recordings at the scene, since the technology is available.

Increasing the common knowledge of the risk of SE upon acute seizures among laymen, ambulance dispatchers in emergency phone call centres, EMS and hospital personnel, generating simplified criteria for suspicion of an imminent SE, transporting SE patients primarily to tertiary hospital and improving EEG availability should be considered as measures to cut down diagnostic delays.

5.4 Treatment response delays

A stepwise definition for treatment response was created for this study in order to characterize the extinction of SE. This included clinical seizure freedom for convulsive cases, obtaining BS for anesthetized cases and return of consciousness for all cases, the latter being the only reliable clinical marker for the end of GCSE. Comparison of our results with previous studies is hampered by the problems in defining the end of SE, as described in detail in review of the literature.

All GCSE cases in our cohort reached the point of clinical seizure freedom during the SE period, the delay of which was nearly equal to previous reported ones[27]. 75 % of the cEEG-monitored patients achieved BS, which was maintained for 12–24 hours, in accordance to current European guidelines[147]. However, the delays in obtaining BS did not reach the time frames recommended by the guidelines, reflecting the clinical reality. The delay in obtaining BS after the start of anesthesia was median 10 hours and accounted nearly half of the total onset-to-BS time. In prospective settings anesthesia-to-BS delay was only 30 minutes regardless of the anesthetic agent[223,224], demonstrating that treatment response delays could be significantly shortened by an acknowledged management protocol and highly trimmed ED team.

We found a significant correlation between early administration of second-stage medication, early clinical seizure freedom, early BS and early return of consciousness. Correlations regarding clinical seizure freedom and BS serve as a

validation of the stepwise definition for the end of SE. Since nearly half of our patients seemed to benefit from early BS, the question remains, whether the proportion of patients with returning consciousness would increase, if third-stage treatment leading to BS would be given in recommended time frames. To our surprise, onset-to-initial-treatment time, onset-to-diagnosis time, and onset-to-anesthesia time were not correlated to markers for cessation of GCSE, nor were the previously established outcome predictors.

Return of consciousness was associated with favorable outcome at hospital discharge. Long delay in onset-to-consciousness was related to poor functional outcome at discharge and in-hospital mortality, which is concordant with a previous study defining the end of SE with clinical recovery[104]. All effort in the management of SE should be made to expedite regaining of consciousness as soon as possible, since slightly less than two days of unconsciousness seems to be a critical time point for the prognosis after SE.

5.5 Strengths and limitations of the study

To our knowledge this is the first study evaluating systematically the delays in the treatment of SE over the whole treatment chain and investigating sequentially the interdependence of the delays and other factors, and their impact on outcome. Retrospective nature of the present study characterizes the clinical reality in SE management, elucidates the difficulties in the treatment chain and enables plausible target setting for protocol streamlining in the future. Abundant pre-hospital patient data were available for each case. Data on time-related parameters was made transparent by careful evaluation and documentation of the coverage and accuracy of delays obtained from the medical documents. However, reporting bias due to inaccurate original recording remains undefined and beyond the control of the research team.

This study encompasses some limitations, which may require caution, when interpreting and generalizing the results. Study material includes a limited number of patients from a single tertiary centre and presents data on mainly non-normally distributed parameters. In studies III and IV only patients with GCSE were included to increase the uniformity of the material. The operational definition of SE has changed since the material collection and therefore SE patients with seizure

duration of 5 to 30 minutes are not included in the study. However, main characteristics of the material (seizure type, etiologies, age distribution) are similar to previously SE published materials. It is remarkable, that the present material weighs toward RSE/SRSE slightly more than previously published ones. This might relate to the changed definition, but another explanation may be that HUCH as a tertiary center collects the most severe cases of SE or that cases with prolonged seizure responding to the first-stage treatment may have missed the diagnosis of SE and are therefore not included in this study.

We also recognize that this study material is rather old. Yet, it is still representative of present-day SE management, since during the last decade no major treatment protocol reformations have been proposed. Rather, less options for AEDs at the time of the material collection and principal use of phosphenytoin as the second-stage-medication reduce bias due to medication heterogeneity.

6 CONCLUSIONS AND RECOMMENDATIONS

This retrospective cohort study reveals the clinical reality in the treatment of SE. After the systematic analysis of delay components in the treatment chain, we found unexpectedly and unacceptably long median delays with a wide range, and acknowledge the need to shorten them markedly (I). These long delays might be related to the remarkable inadequacy detected in recognition of SE both among laity and medical professionals, and suboptimal triaging of SE patients. There is an obvious need for increasing awareness of imminent SE and streamlining the pre-hospital management of established SE. SE should be given a compeer position with stroke and cardiac infarction and acknowledged as a medical emergency with similar resource allocation in the pre-hospital management (II).

Delays in the treatment chain might be more significant determinants of GCSE cessation than the previously established outcome predictors (III). Nearly all main components of the treatment chain have significant associations with functional outcome and mortality at hospital discharge. However, none of them seem to be independently associated with outcome, which impresses the dynamism of the treatment of GCSE (IV). Therefore, streamlining the whole treatment chain of SE is advocated, although the main focus should be on pre-hospital management.

According to the results of this thesis, the following amendments to the management protocol of SE are recommended:

- Triaging suspected SE cases with highest priority
- Recruiting physician-based EMS units upon primary alarm
- Qualification of paramedics to intubate and stabilize the patient already at the scene
- Administration of second-stage medication out-of-hospital
- Standardized pre-hospital management protocol for established SE
- Transportation of SE patients exclusively to hospitals with neurological expertise
- Generation of simplified criteria for suspicion of an imminent SE applicable both out-of-hospital and in health care units

We further advocate:

- Investigation of diagnostic possibilities on emergency site
- Increased education to improve common knowledge of the risk of SE among acutely seizing patients

We suggest that delays are considered as endpoints in planning future prospective study protocols, which should include matched patient groups.

7 ACKNOWLEDGEMENTS

The work for this dissertation started in 2004 as a thesis for graduation from Medical school. It was 2011 until I adopted a thought of conducting an academic dissertation. Through these years this study was carried out in Helsinki University Central Hospital in Neurological department.

I owe my sincere gratitude to my supervisor, professor Seppo Soinila, for his long lasting support, patience and belief in me and in this Thesis. His ability to ensure a coordinate atmosphere in discussions, where no questions were too simple to ask, was crucial in raising novel and inspiring research questions. I also would like to thank him for numerous conversations about medicine, science and life over these years.

I wish to thank Associate Professor Harri Mustonen for collaboration and patient guidance in statistical matters. His reliable calculations and extensive knowledge in statistics facilitated conducting this study.

I thank co-authors MD Kaisa Kotisaari and my brother MD Jaakko Ritvanen. Thank You Kaisa for endless discussions, sharing same enthusiasm for developing systems and peer support during the growth into specialist in Neurology. Thank You Jaakko for being such a great brother and for the courage of being the first student under my supervision, when working on your graduation thesis in Medical school. I have enjoyed our discussions about research and beyond and I dare to wish more in the future.

I am thankful to Professor Stephan Rüegg and Associate Professor Tobias Loddenkemper for conducting the preliminary examination of this Thesis and for giving such encouraging comments. Additionally, I thank the members of my Thesis follow-up group, Docent Merja Soilu-Hänninen and Doctor Marjaana Tiainen, for cooperation.

I am grateful to HUCH neurological department for the flexibility in organizing time for making research and for the Research Grants from Hyvinkää Hospital, Helsinki University Central Hospital, Epilepsy Research Foundation in Finland, Maire

Taponen Foundation, Brain Foundation of Finland and Finnish Medical Society Duodecim.

I thank all my relatives, friends and colleagues for encouraging and supporting me during this process. Special thanks go to other PhD candidates along the way for peer support.

I thank my siblings, Hanna, Antti and Jaakko, for being there for me. We are privileged for having such a solid confidence and esteem between us. I am thankful to my parents-in-law, Eila-Riitta and Armas, for trustworthy support and immeasurable assistance with the challenges of everyday life. I also would like to thank my parents, Annukka and Hannu, for endlessly loving and believing in me and caring of my wellbeing. Your advice in the planning phase of this study, encouragement during the hardest times and engrossing debates of fundamentals in science have made finishing this Thesis possible.

Finally, I would like to show deepest gratitude and love to my family. Antti, You are my soul mate, love of my life and the best imaginable father to our children. We share same passions in life and together we form an incredible team. In addition to all the mental support You have given, the technical assistance (especially with excel) has been imperative to accomplish this project. Salla, Lotta and Nuutti, You make my life worth living. Thank You for Your tolerant relation to this project, finally it is over. I love You.

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